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MILD FORMS OF CORONARY THROMBOSIS¹

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NEW YORK

In reviewing the history of the knowledge concerning acute coronary obstruction, it is remarkable that the first publication that satisfactorily correlated symptoms, signs and pathologic data has been overlooked, for the most part. In 1884, in the *Zeitschrift für klinische Medizin*, Leyden¹ gave an excellent account of coronary sclerosis and thrombosis in a paper entitled "Ueber die Sclerose der Coronar-Arterien und die davon abhängigen Krankheitszustände." It is to the Russians, Obiastzow and Strasesko,² who published an article in the same journal in 1910 that credit is usually given for the description of the clinical features. These authors were able to make a correct antemortem diagnosis in two of the three cases reported by them. In Europe, however, very little interest was aroused by these publications, and their importance for clinical medicine was unrecognized. It was in 1912 that Herrick,³ in his classic paper on "Clinical Features of Sudden Obstruction of the Coronary Arteries," called the attention of the medical profession in America to the disease. It is not my purpose at this time to trace the development of this knowledge. A brief review may be found in Levine's recent monograph.⁴

In the delineation of any new clinical picture, it is the rule that the more severe and typical varieties of the condition are first recognized and described. The reasons for this are obvious. A number of symptoms and signs are observed, which, when found in association with certain functional and anatomic disturbances, are proved to be characteristically diagnostic. More exact methods of examination often serve

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¹ From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Medical Clinic of the Presbyterian Hospital.

* Read by title at a Meeting of the Association of American Physicians, Atlantic City, N. J., May 7, 1930, and before the New Haven Medical Society, May 21, 1930.

1 Leyden, E. Ueber die Sclerose der Coronar-Arterien und die davon abhängigen Krankheitszustände, *Ztschr. f. klin. Med.* **7** 459 and 539, 1884.

2 Obiastzow, W. P., and Strasesko, N. D. Zu Kenntnis der Thrombose der Koronararterien des Herzens, *Ztschr. f. klin. Med.* **71** 116, 1910.

3 Herrick, J. B. Clinical Features of Sudden Obstruction of the Coronary Arteries, *J. A. M. A.* **59** 2015 (Dec. 7) 1912.

4 Levine, S. A. Coronary Thrombosis. Its Various Clinical Features, *Medicine* **8** 245 (Sept.) 1929.

to define the picture with even greater precision. A specific etiologic factor may be found. The course of the disease is followed over a period of years, its complications and sequelae are noted, and eventually it becomes possible to evolve prognostic criteria, both immediate and remote. The atypical and milder forms of the picture at first escape recognition. Later, greater familiarity with the possibilities of variation from the standard pattern directs attention to cases with less striking and more unusual features.

This clearly has been the course of events in the history of coronary thrombosis. It was naturally the fatal cases, in which necropsy observations could be checked against clinical manifestations, that first served to outline the picture. Patients with the more severe symptoms, even though they recovered, next claimed attention. But in his first paper, in 1912, Herrick said: "In a third group may be placed nonfatal cases with mild symptoms. Slight anginal attacks without the ordinary causes (such as walking), perhaps some of the stitch pains in the precordia, may well be due to obstruction of small coronary twigs." Having given much thought to this subject for many years, Herrick, in 1929, before the Association of American Physicians, called attention to some unsolved problems connected with acute obstruction of the coronary arteries.⁵ I quote him again: "How often do mild types of the accident occur? There are mild cases, mild as to onset, as to early symptoms and late effects.

That these cases are of greater frequency than is generally recognized is almost certain. That these mild cases with prompt recovery are really of the nature of coronary thrombosis is at times shown by the fact that later the clear cut attack of severe form may occur, recognized by patient and doctor as of the same character as the earlier mild one, differing chiefly in degree. In what way may these cases be recognized more definitely? By what grouping of historical data, symptoms, signs and instrumental findings, may we be able to state that this accident has occurred?" It is with the hope of supplying at least partial answers to queries such as these that the following cases are described and discussed.

In all of the eight cases selected for analysis the patients were seen in office or consultation practice, and their records are sufficiently detailed so that there can be but little doubt concerning the nature of the illness. That such patients are found with relative infrequency in the wards of a hospital is not remarkable, since the symptoms are apt to be of short duration, the degree of incapacity is often not great and, if help is needed, a neighborhood physician is called. At the time of the attack, medical advice may not be sought. It seems likely that the condition is frequently not recognized.

Five of the case histories will be given in full.

⁵ Herrick, J. B. Some Unsolved Problems Connected with Acute Obstruction of the Coronary Arteries, *Am Heart J* 4:633 (Aug) 1929.

REPORT OF CASES

CASE 1—History—A man, aged 41, a journalist, married, complained of pain in the left arm and in the jaw, induced by exertion. His father and mother had died at the age of 65 of "angina pectoris." The patient had enjoyed good general health. Five years before, he had cholera while in Serbia, and was in a hospital for five weeks. Later, he was treated in the American Hospital in Paris for ulcers of the intestine, and he had been well since then. He did not drink coffee or alcohol, but he had smoked fifty or more cigarets daily until the onset of the present illness.

Symptoms began a month before his visit with sudden pain in the left arm which came on while he was playing bridge. The arm felt as though it had been struck. The pain persisted, and the following day he consulted a physician who told him that he had neuritis. Examination of the teeth, tonsils and sinuses revealed no focus of infection, and a Wassermann reaction of the blood was negative. Five days later, while the patient was walking on the street, the arm hurt so severely that he had to stop, he went to bed. Medication afforded some relief, and the following day he was able to be out and about. Since that time paroxysms of pain recurred whenever he walked, and were associated with aching in the jaw. There was no pain in the chest, nor had he noted dyspnea or palpitation. He was advised to avoid effort, and to take his work more easily. He clearly associated the discomfort with physical effort.

Examination—The patient was nervous, pasty-looking and introspective and was much concerned about himself. There was no dyspnea or cyanosis. On percussion, the heart was found to be slightly enlarged to the left. The rhythm was regular, the rate, 88. The sounds were weak, there were no murmurs, and no gallop rhythm was heard. The peripheral vessels were barely palpable. The blood pressure was 124 systolic and 70 diastolic. On fluoroscopic examination, the heart was seen to be distinctly enlarged, to both the right and the left. Its pulsations were not vigorous. There was slight diffuse dilatation of the aorta. Measurement of the orthodiagram showed a total transverse diameter of 15 cm. with an internal diameter of the chest of 24.4 cm. The electrocardiogram (fig. 1) showed regular sinus rhythm, with a ventricular rate of 74. There was moderate left ventricular predominance. The P-R (conduction) time was 0.19 second. The noteworthy features of the record were inversion of the T wave in leads II and III, and the presence of a markedly exaggerated Q wave in the third lead. The character of the inversion of the T wave particularly the deep V-shaped T wave in lead III, and the prominent Q wave in the lead afforded definite signs of myocardial damage. Taken in conjunction with the history and the finding of cardiac enlargement, they made possible a diagnosis of coronary sclerosis, and gave striking presumptive evidence of thrombotic closure of a small branch, with infarction of the myocardium.

Course—The patient was first seen two and one-half years ago, and since that time had lived in Paris. From his physician, I learned that he continued to have some discomfort for a period of months, but has lately been able to carry on restricted activities without symptoms. He has been careful to live within the limits of his physical capabilities.

CASE 2—History—A married man, aged 48, a real estate operator, complained of precordial pain radiating to both arms, for the past three or four years. His father had died suddenly in bed, at the age of 52. One brother had died at the age of 35, of heart disease. The patient had enjoyed exceptionally good health. At 39 (eight years previously) he had had pneumonia, followed by empyema. A

rib was resected and the pleural cavity was drained, he was ill for four months, but made a complete recovery. Appendectomy had been done twenty years previously. Roentgenograms had recently been taken of the teeth, and they were said to be free from infection. He smoked a pipe almost constantly—perhaps thirty pipefuls each day. He took no coffee or alcohol. Before the onset of cardiac pain, he was physically very active, playing tennis, swimming, rowing and running, without distress of any kind.

About four years before his visit, he first noted precordial pain on walking, radiating down both arms, but more to the left. Gradually, he observed that less and less effort induced the discomfort, and eight months before examination he was unable to walk a block without stopping. At that time he had an attack

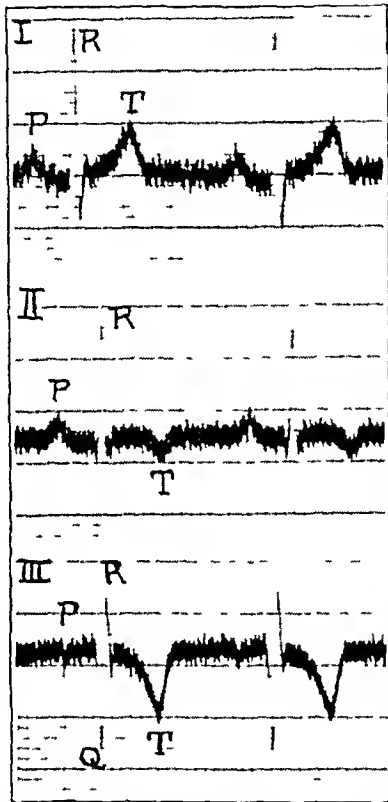


Fig 1 (case 1)—T. type curve with V-shaped T wave in lead III, suggesting closure of a branch of the right coronary artery. Q_3 is strikingly prominent.

that was called "acute indigestion" characterized by intense pain in the epigastrium but unassociated with nausea or vomiting. He felt as though he would suffocate. He was told that his pulse was rapid. He was in bed for three days and remained at home for the remainder of the week, because of a sense of exhaustion. The blood pressure at the onset of the attack was said to be 160 systolic; one week later it was found to be 110. Since this attack he had improved considerably, and was better than he was before it occurred. He now experienced pain on strolling after he had gone about half a mile. Slight hurrying made him stop after four or five blocks. Distress was more acute if he made an effort after eating. The pain was sharp, but disappeared entirely about one-half minute after the cessation of effort. There had been no dyspnea. He had taken no medicine recently.

Examination—On examination, the lips were found to be slightly cyanotic. The retinal vessels showed moderate sclerosis. On percussion the heart was found to be slightly enlarged to the left. The rhythm was regular, the rate, 76. At the apex, the first sound was of normal quality and intensity. Toward the sternum, it had a metallic tone and was slightly slurred. There was no accentuation of the aortic second sound. The peripheral vessels were just palpable. The blood pressure was 122 systolic and 74 diastolic. There was no enlargement of the liver or spleen. The Wassermann reaction of the blood was negative. A

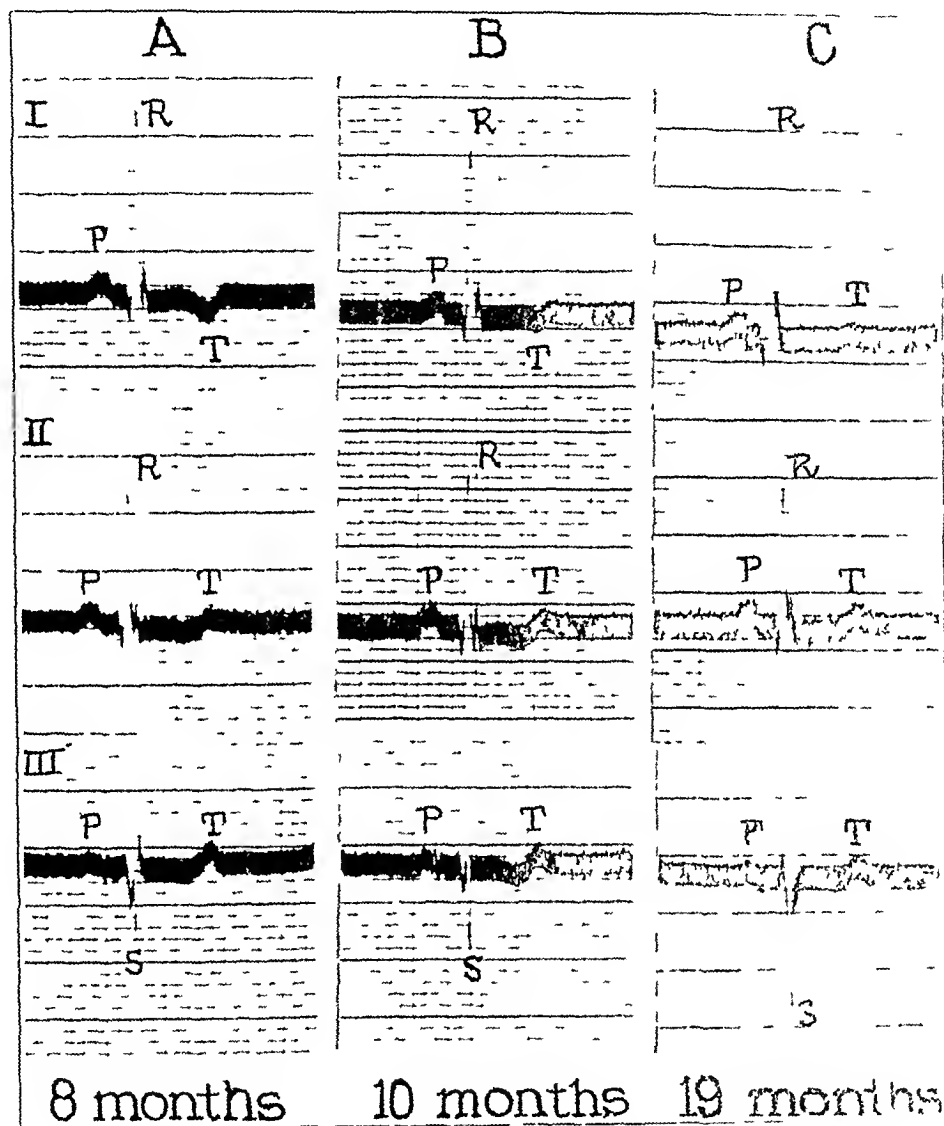


Fig 2 (case 2)—A shows T_1 type curve, denoting closure of a left coronary branch, persisting for eight months after the attack. B, inversion of T wave marked, and C, T wave now upright in all leads.

blood count and chemical examination of the blood showed normal results. On fluoroscopic examination, the heart was seen to be a little enlarged both to the right and to the left. The total transverse diameter in the orthodiagram was 14.6 cm, the internal diameter of the chest being 25.5 cm. There was no dilatation of the aorta. The electrocardiogram (fig. 2) showed regular sinus rhythm with a ventricular rate of 74. The P-R (conduction) time was 0.14 second. The T wave was inverted in leads I and II, and diphasic in lead III. There was

moderate left ventricular preponderance. The noteworthy observations were inversion of T_1 and partial inversion of T_2 . Such inversion of the T wave is often seen in coronary sclerosis, and in this case it was taken to represent residual evidence of a small myocardial infarct.

The patient was advised to take 0.1 Gm of euphyllin (theophylline ethylenediamine) at first four times a day, then three times daily, after meals. He was seen at intervals, the last examination having been made one year after his first visit. At that time, he stated that he was distinctly better. He had accustomed himself to a modified kind of life, which he accepted philosophically. Hurry, worry and excitement still caused precordial pain and a sensation of numbness in the arms. He took a five months' holiday during the summer, and during this time he rarely had discomfort except when emotionally upset. He had never found it necessary to take nitroglycerin. He went in for an occasional dip in Long Island Sound during the warm weather, and since his return from his vacation had been working hard and steadily.

The last examination of the heart showed no change in size or signs. There was no gallop rhythm. The blood pressure was 136 systolic and 88 diastolic. The electrocardiogram taken two months after his first visit (ten months after the coronary closure) showed definite changes as compared with the first record. The T wave in lead I was less sharply inverted and T_2 was more markedly diphasic. The P-R (conduction) time was 0.13 second. The changes were slight, but were in the direction of normal. The record taken one year after the first visit (one year and eight months after the attack of thrombosis) showed regular sinus rhythm, with a ventricular rate of 72. The P-R (conduction time) was 0.12 second. The T wave in all leads was now upright. The change was again in the direction of normal, and appeared to indicate healing of the small area of myocardial infarction. The changes as compared with the original record were marked.

Summary—An attack of "acute indigestion," with substernal and epigastric pain, occurred in a man of 47, who had had precordial pain on effort for about four years. He was in bed for three days and at home for the remainder of the week. Following the attack, he improved steadily, although cardiac pain could still be induced by effort or excitement. The electrocardiographic changes over a period of a year indicated healing of the area of infarction. Cardiac enlargement suggested the existence of coronary sclerosis and myocardial fibrosis probably for several years prior to the acute attack.

CASE 3—History—A merchant, aged 37, married, was seen four days after his first attack of cardiac pain. His father and mother had both died of "angina pectoris," at the age of 76. His ancestors on the maternal side were said to be subject to heart disease, but died at an advanced age. Except for numerous sore throats, for which tonsillectomy had been performed twenty years before, he had enjoyed remarkably good health.

He had always been a large man, at one time weighing 300 pounds (136 Kg). He worked hard, was an active speculator on the Stock Exchange, drank freely, smoked heavily and went out considerably at night. He had not taken a vacation in over a year. For a number of years his blood pressure had been in the vicinity of 180 systolic and about 100 diastolic.

While at his office, sitting at his desk, he suddenly had an attack of severe substernal pain, radiating to the left arm, which persisted for about six hours. There was no nausea or vomiting. He consulted his physician, who immediately took him home and put him to bed. His color was said to be ashen. The systolic blood pressure had fallen to 140. He was given a hypodermic injection of morphine and passed a comfortable night.

He was seen by me at his home four days after the attack. He felt well, and greatly resented being kept in bed. The systolic blood pressure was still 140. There was a faint gallop rhythm at the apex. He remained at home for one week and then returned to his business, going to the office for a part of each day. He used less tobacco and alcohol.

Examination—He came to my consulting room two weeks after the onset of the illness. He weighed 224 pounds (101.6 Kg), which was 50 pounds (22.7 Kg) over his calculated weight. He was pasty in color. There was no dyspnea.

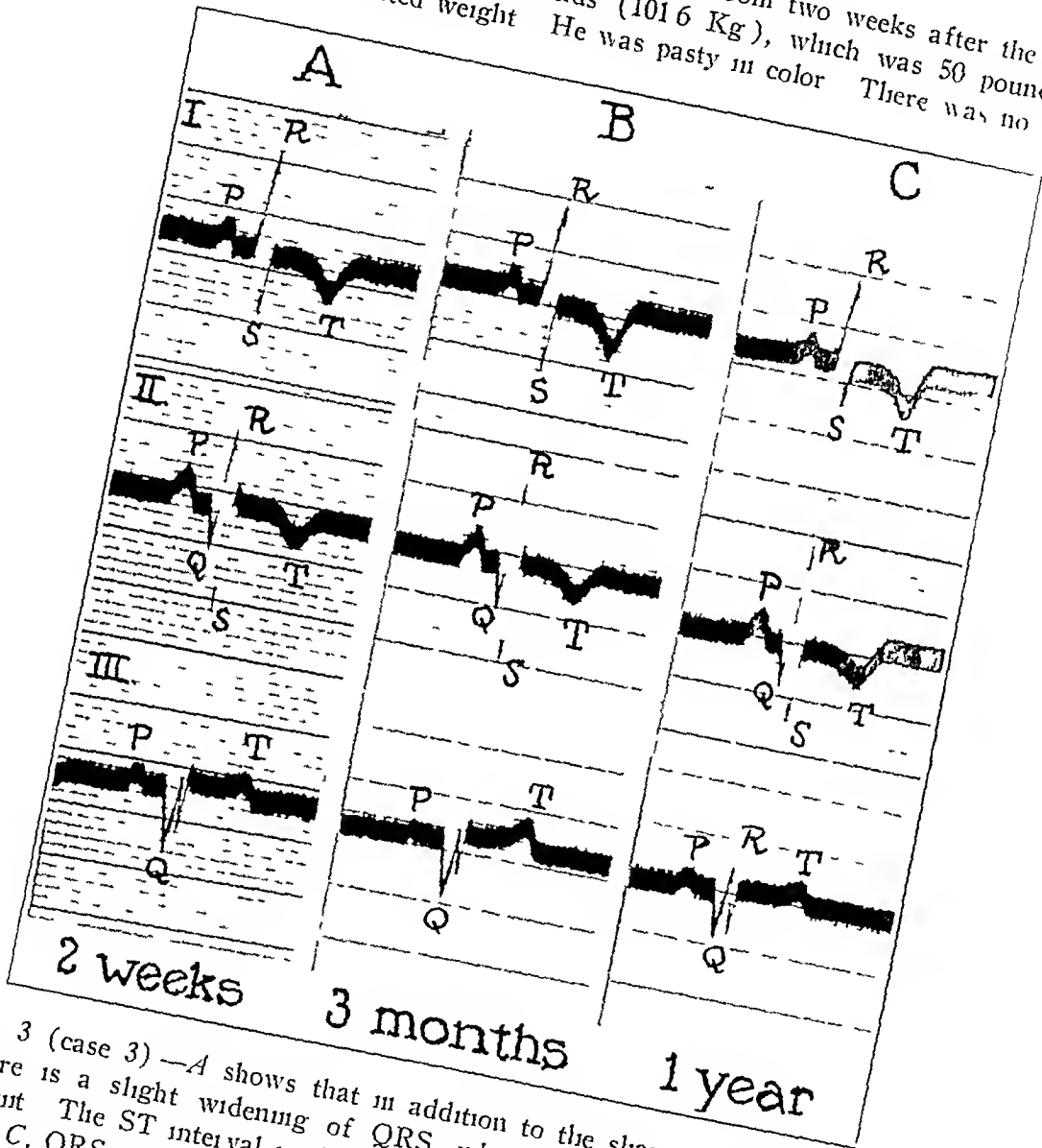


Fig 3 (case 3)—A shows that in addition to the sharp inversion of T_1 and T_2 , there is a slight widening of QRS, which measures 0.11 second. Q_3 is prominent. The ST interval is elevated in leads II and III. B shows T_1 a little deeper. C, QRS is now within normal limits, the ST interval in leads II and III is no longer elevated.

or cyanosis. The retinal vessels were normal, and the peripheral arteries were barely palpable. The heart was moderately enlarged. No gallop rhythm was heard. There were no murmurs. The blood pressure was 148 systolic and 96 diastolic. On fluoroscopic examination, the heart was seen to be of good size, though only slightly enlarged in relation to the internal diameter of the chest. The aorta was not dilated, but was tortuous for a man of his age. The electrocardiogram (fig 3) showed regular sinus rhythm with incomplete bundle branch

block. The ventricular rate was 80. The QRS interval was 0.11 second. There was a moderate degree of left ventricular preponderance. The P-R (conduction) time was 0.14 second. The T wave was sharply inverted and of the V type in leads I and II, and upright in lead III. These changes afforded evidence of myocardial injury, and were suggestive of infarction following coronary thrombosis.

Course—The patient was seen again three months later. He had been going to business, and had played golf without any symptoms referable to the heart. He had not maintained the dietary restrictions outlined and had not lost any weight. He went out less at night, smoked but little and almost entirely stopped drinking. He continued to go to night clubs and danced. He had taken no medicine. Examination at this time showed the heart sounds to be definitely weak. A short systolic blow had appeared at the apex, and the aortic second sound had taken on a somewhat ringing quality. The blood pressure was 142 systolic and 92 diastolic. The size of the heart, as measured on roentgen examination, was unchanged. The electrocardiogram showed the T wave in lead I to be a little deeper and T₊ higher, but the record otherwise resembled the one taken three weeks earlier.

He was next seen nine months later. He had spent the summer in Europe, where he took a cure at Marienbad. He played golf, nine holes at first, later eighteen holes each day, without discomfort. On two occasions, he became tired and short of breath, but not, he thought, following a game of golf. There was no recurrence of cardiac pain. He had resumed dancing, was working as hard as ever and smoked twenty cigarettes and two cigars each day. Examination showed the weight to be 230 pounds (104.3 Kg.). He still looked pasty. The size of the heart was unchanged. The rhythm was regular, the rate, 72. The first sound at the apex was now slightly split and impure. The general quality of the sounds was fairly good. The blood pressure was 154 systolic and 104 diastolic. The electrocardiogram showed regular sinus rhythm, with a rate of 72. The left ventricular preponderance was still present. The P-R (conduction) time was 0.15 second. The intraventricular conduction time was now within normal limits, being 0.09 second. The ST interval in leads II and III was no longer elevated. The T waves still had the pointed V shape in leads I and II. The record suggested a healed myocardial infarct, with, however, residual permanent injury to the heart muscle.

Three months later, and almost exactly a year after the first attack, the patient again experienced moderate substernal pain, for which he consulted his physician. This passed off in the course of a few minutes, and he continued his usual routine. Three days later he had a sharp pain radiating to the left arm, but unaccompanied by nausea or vomiting, and persisting for several hours. He came home from his office and went to bed, and was given $\frac{1}{2}$ grain (0.032 Gm.) of codeine by his wife. I saw him the same evening. This time, his color was distinctly ashen, and he was genuinely concerned about himself. The heart rate was 72, the rhythm regular. The blood pressure was 174 systolic and 100 diastolic. No gallop rhythm was present. He was given a hypodermic injection of morphine, and was advised to remain in bed. Thus he did, although he insisted on getting up to go to the bathroom. He continued also to keep actively in touch with his broker's office, and became considerably excited because of the changes in the stock market. Six days later, he had a recurrence of the substernal pain, which radiated to both arms. On this day, the blood pressure was 148 systolic and 85 diastolic, and slight fever appeared, the temperature persisting in the vicinity of from 100 to 101 F. for six days. The leukocyte count at this time was 15,000,

with 76 per cent polymorphonuclears. No friction rub was heard, and there was no cardiac arrhythmia. The electrocardiogram showed regular sinus rhythm. The only change since the record taken a month previously was a slightly shallower T wave in leads I and II. On this occasion there was no increase in intraventricular conduction. Two weeks after the onset of the second attack, the only change on examination was the fall in blood pressure to 132 systolic and 80 diastolic. Against his will, the patient was kept in bed for three weeks. At the time of writing this article (about three months after the attack), he was again at work, but was taking better care of himself.

CASE 4—History—A man, aged 41, a lawyer, married, was brought to me for examination by his physician because of an attack of substernal pain that had occurred five days before. He had always been an active, intense worker. For twenty years, he had had recurring sinus infections. He had never been acutely ill, nor had there been any cardiac symptoms prior to the onset of the present attack. This began suddenly five days before his visit, with excruciating substernal pain, radiating to both arms and to both clavicles. Ordinary sedatives, such as bromide, were ineffectual, and $\frac{3}{4}$ grain (0.048 Gm.) of morphine was necessary to make him comfortable. He was not nauseated, nor did he vomit. The heart rate was rapid, but there was no disturbance in rhythm. He remained in bed until the following day, and by this time the blood pressure, which usually was in the vicinity of 140 systolic, had fallen to 90. There was still some soreness across the chest, but no acute pain. The chemical analysis of the blood and urinalysis gave normal results, and the Wassermann reaction of the blood was negative. He remained quietly at home for five days.

Examination—The patient was large and well built, his color was good, and he was able to lie flat without discomfort. The size of the heart was normal. The rhythm was regular, the rate, 68. The sounds were of fairly good quality, having perhaps a slightly valvular quality at the apex, where there was a short, blowing, systolic murmur. No gallop rhythm was heard, and there was no accentuation of either second sound at the base. The peripheral vessels were just palpable. The blood pressure was 110 systolic and 66 diastolic. The liver was not enlarged, and there was no edema. On fluoroscopic examination, the heart was seen to be of the vertical type. It was normal in size and shape, and there was no dilatation of the aorta. The electrocardiogram (fig 4) showed regular sinus rhythm, with a ventricular rate of 68. The P-R (conduction) time was 0.16 second. The T wave was slightly inverted in lead II and markedly inverted and of the V type in lead III. The Q wave in lead III was strikingly prominent. A diagnosis of thrombosis of a coronary artery was made, and in view of the rapid recovery, the inference was drawn that a small branch had been occluded.

Course—Ten days following his visit to me, the patient sailed for Europe, where he took three months' rest from business. In Paris, he was examined by Dr. Vaquez and Dr. Bordet, who repeated the examinations and confirmed the observations. He never experienced any further pain in the chest. For the first two months after the acute illness, he noted some shortness of breath on effort, but this gradually disappeared and did not recur.

The patient was seen again a little more than four years after the first attack. Eight months previously several infected teeth were removed because they were protruding into the right antrum. Subsequently, a radical operation was performed on the antrum, and the jaw bone was curetted. This series of infections and operations caused a "fluttering" and racing of the heart. He observed a distinct relationship between the flaring up of the infection in the antrum and the

attacks of palpitation and tachycardia. There was no cardiac pain or dyspnea during the sinus attack. He lost considerable weight and felt bad generally. In the four year interval he had worked regularly except during this illness eight months ago. He also played golf without discomfort. He was leading a normal life and considered himself well.

Four years after the acute attack, examination showed the size of the heart to be unchanged. The rhythm was regular, the rate, 76. The sounds were of fair

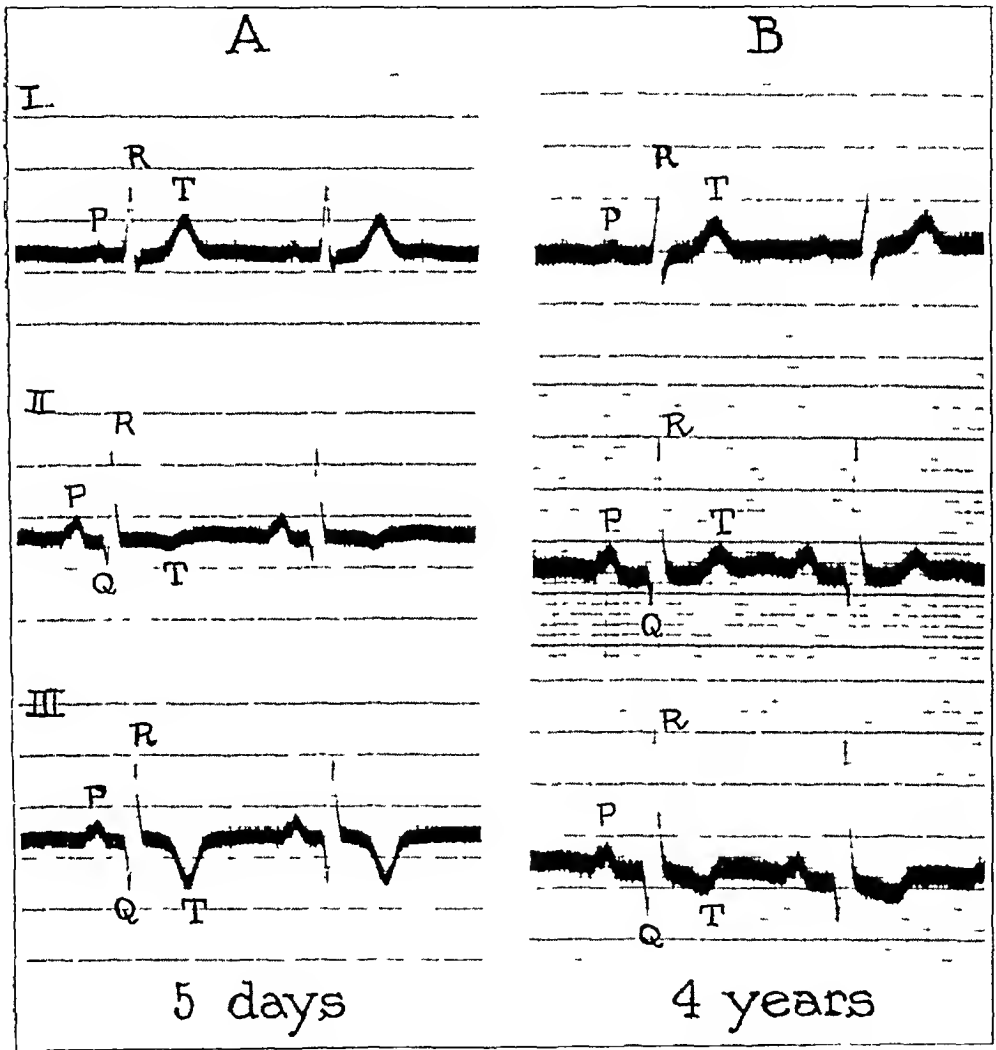


Fig 4 (case 4) —A shows T_a type curve with prominent Q_s , B, T_s still inverted, T_r now upright. Q remains prominent.

quality, though not strong, and the aortic second sound was relatively enfeebled. The peripheral vessels seemed a little thicker than on the previous examination. The blood pressure was 132 systolic and 76 diastolic. Fluoroscopic examination gave results that were the same as those obtained at the time of the first visit. The electrocardiogram showed regular sinus rhythm, with a ventricular rate of 76. The P-R (conduction) time was 0.19 second. The T wave was upright in leads I and II and inverted in lead III. There was slight notching of the R

waves in leads II and III Compared to the record made four years earlier, quite marked changes were evident In lead I the T wave was a little lower, though this was not striking In lead II, the RT interval was slightly concave instead of slightly convex, and the T wave was upright instead of inverted In lead III, the Q wave was still present T_r was still inverted, though less deep, and not of the V type The voltage was distinctly higher in leads II and III

Summary—Clearly this patient had a thrombotic closure of a small coronary branch with infarction of the heart muscle Healing was apparently rapid The only symptom during the convalescent period was dyspnea on effort, which passed off in the course of two months There was never a recurrence of pain The myocardium was apparently irritable, since it was stirred up by a succession of sinus infections and operations on the head, although this may occur in hearts otherwise apparently normal The electrocardiographic changes indicated healing of the infarct with residual scarring

CASE 5—A married man, aged 48, a builder, was seen because of substernal pain His father died at the age of 51, of Bright's disease One brother died at 42, of nephritis with hypertension The patient had had diphtheria in childhood He was subject to sore throats and had recurrent sinus infections, for which continued treatment, with occasional puncture of the antrum, was carried out He smoked eight cigars a day and took alcohol only occasionally He worked at high tension, and his hours at the office were long

While playing golf and walking off a tee, he had a sudden sense of substernal pain, as though a lump were there This sensation lasted about fifteen minutes, but was not really troublesome, and he finished his game During the following four days he was well Then, after lunch, he had a similar, though more severe, pain, and felt as though he were strangling The pain radiated down both arms to the fingers He was weak and would have fallen had he not been caught by a friend He was placed on a couch, and was quite uncomfortable for about half an hour He vomited once He went home and to bed, where he remained for two days with slight fever The pain over the upper part of the precordium and in the left shoulder persisted for several days, though with diminished intensity He did not return to work, and came in for examination ten days after the episode that occurred on the golf links, complaining of pain in the substernal region on moving about and weakness Dyspnea and palpitation were absent throughout

Examination—The temperature was 99.8 F, by mouth The size of the heart was normal The rhythm was regular, the rate, 92 There was a faint pre-systolic gallop rhythm at the apex There was no thickening of the peripheral vessels The blood pressure was 126 systolic and 80 diastolic On fluoroscopic examination, the absence of cardiac enlargement was confirmed, and no dilatation of the aorta was made out The Wassermann reaction of the blood was negative A diagnosis of coronary thrombosis was made, and the patient was advised to go home and remain at rest Against advice, he returned to work two weeks after the onset of the illness He gave up smoking, and never took it up again

Course—The patient was seen at frequent intervals during the next four and one-half years He resumed golf two months after his first visit to me He was unwilling to believe that he had had a serious heart attack, and plunged actively into the work of his business After an interval of six months, a gallop rhythm was still heard At times, he had a slight twinge in the region of the precordium or a tight sensation across the chest, but he continued to play thirty-six holes

of golf without discomfort. Substernal oppression was noted, particularly after meals or when excited. Infection in the antrums persisted, and local treatments were carried on. He continued his normal life, hard work and week-ends of golf, in spite of repeated warnings that it would be wise to take matters more easily.

Four and one-half years after his first cardiac symptom, while walking to the railroad station, the patient had a sudden, sharp, substernal pain, radiating to the left arm. He hailed a taxicab, returned to his home and went to bed. There was no nausea or vomiting. The pain persisted, and he called in a physician, who gave him a hypodermic injection of morphine. I saw him about three hours later. He was fairly comfortable, not cyanotic and mentally clear. The heart rate was 100, the rhythm regular. There was no gallop or pericardial friction. The blood pressure was 140 systolic and 100 diastolic. The temperature, by mouth, was 99.2 F. He was given another $\frac{1}{4}$ grain (0.016 Gm) of morphine, and was taken to the hospital in an ambulance.

On admission, the leukocyte count was 20,000, with 90 per cent polymorphonuclears. The urine contained a trace of albumin. On the following day, the temperature rose to 102 F and remained at this level, with slight variations. A friction rub was heard close to the sternum in the third left space, and a gallop rhythm appeared and persisted. The heart rate remained elevated, being from 110 to 120 per minute. There was slight cyanosis of the lips. The patient was cheerful, mentally clear and relaxed. At times he complained of substernal pain, but this was readily controlled by sedatives. Fever and tachycardia, however, continued, and on the fifth day after admission to the hospital, at midnight, he suddenly complained of an unusually sharp substernal pain, and within a minute gave a gasp and was dead. Necropsy was not permitted, but the manner of death suggested rupture of the left ventricle.

The electrocardiograms of this patient are of particular interest, because they give a running record of events (fig 5). The first record, made ten days after the initial attack, showed slight elevation of the RT interval in leads I and II, and flattening of T_2 . Two months after onset, T_1 was inverted and followed a convex RT interval. The convexity of RT in lead II was a little less marked, and T_2 had become definitely upright. After six months, T_1 was again upright, and the RT interval in lead I was no longer convex. T_2 and T_3 were likewise upright, and the curve was essentially normal. During the following three years, there was no noteworthy change in the form of the curves. The last record was taken on the second day of the terminal attack. It shows strikingly the depression of the RT interval in lead I and the high origin of other portions of the curve connecting R and T in leads II and III. A prominent Q wave is also visible in the third lead. The record is quite characteristic of infarction of a considerable area of the myocardium.

Summary—A man, aged 48, previously in excellent health, had a mild attack of coronary thrombosis, which confined him to his home for three days, and enabled him to return to work at the end of two weeks. Electrocardiographic changes confirmed the nature of the attack. He made a rapid recovery, and for a period of four and one-half years led a normal, active life, and played golf. During these years, he had occasional twinges of substernal pain, but not severe discomfort. The electrocardiograms gave no evidence of progressive myocardial disturbance. The terminal attack was more severe in onset, and death occurred suddenly on the fifth day, in all probability due to rupture of the left ventricle.

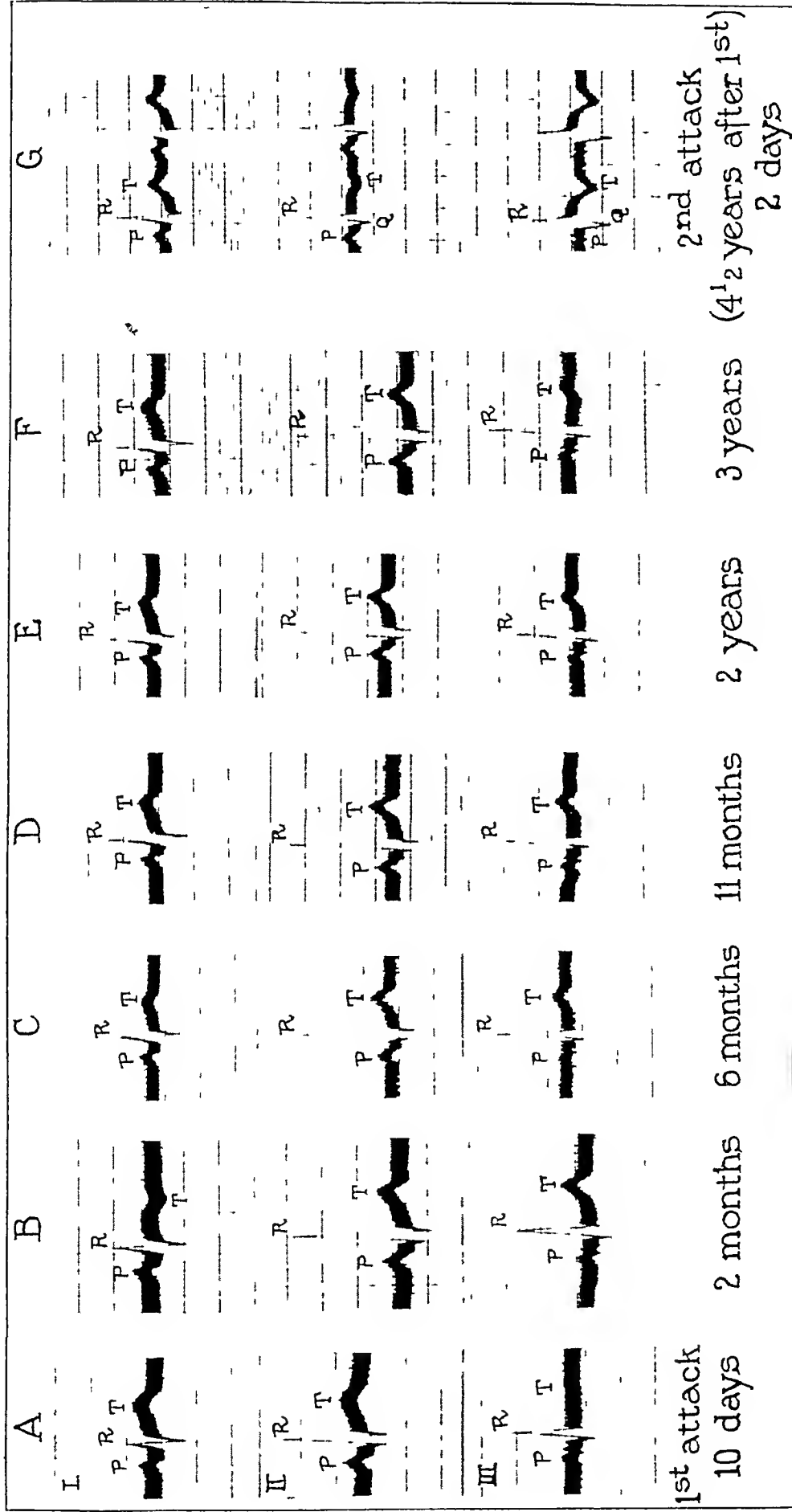


Fig 5 (case 5) — I shows a slight elevation of ST interval in leads I and II, and a flattened T, B, T₁ is now inverted and T₂ is upright, C, I is upright in all leads, D, E and F, little change during a period of three years, and G a depression of the RT interval in lead I and an elevation in leads II and III. Q₂ is prominent. T₂ and T₃ are inverted. The patient died three days later.

Analytic Summary of Eight Cases of Mild Coronary Thrombosis

Age	37, 37, 41, 41, 45, 48, 48, 48 (average 43 years)	Rate of Recovery—Continued			
		12 hours, 24 hours			1
Sex		(Same patient in two attacks, after first attack, took 2 hour train trip to New York)			
Male	7	2 days			2
Female	1	(One at home 10 days, one "still a little weak" at this time)			
Family History		3 days			1
"Angina pectoris"	3	5 days			1
Sudden cardiac death	2	(Sailed for Europe on fifteenth day)			
Hypertension and nephritis	1	4 days, 10 days			1
Previous Cardiac History		(Same patient in two attacks)			
Pain on effort	2				
Hypertension	2				
Heart murmur (following streptococcus sore throat)	1				
History of Infections		Signs	Pres ent	Ab sent	Not Known
Cholera (5 years before)	1	Cardiac enlargement	5	3	0
Recurring sinus infections (1 for 20 years, 1 for "many years")	2	Cardiac irregularity	1	7	0
Streptococcus sore throat followed by heart murmur 25 years before renal infection with two operations 5 years before	1	Fall in blood pressure	5	0	3
Pneumonia and empyema (8 years before)	1	Fever	4	0	4
Rheumatic fever 37 years before, no cardiac involvement	1	Leukocytosis	2	1	5
Colitis	3				
Syphilis	0	Electrocardiographic Changes			
Excessive use of tobacco	6	Present			6
Obesity (associated with hypertension)	1	Absent			2
Symptoms of the Attack		Character of Changes			
Substernal pain	5	T ₁ type (left coronary involvement)			3
Vomiting	3	T ₂ type (right coronary involvement)			2
Epigastric pain, called "acute indigestion"	1	Incomplete bundle branch block			1
Pain in left arm and jaws	1	Prominent Qs			4
Dyspnea (with pain)	1	Elevation of RT only			1
Precordial oppression, without pain, but with nausea	1	Subsequent Course			
Rate of Recovery (measured by patient's desire and ability to resume his usual activities)		Living			7
12 hours	2	4 years			1
(One never bedridden, one went to physician's office following morning)		2½ years			1
		1 year			4
		6 months			1
		Dead (4½ years after first attack)			1
		Degree of Restoration of Function after Attack			
		No symptoms, full activity			2
		No symptoms, restricted activity			2
		Symptoms present (Pain, 2, dyspnea, 1)			3
		Subsequent Attacks			3
		1 after 4½ years (fatal)			
		1 after 1 year			
		1 after 3 months, and again 6 months (The two youngest patients, each 37)			

ANALYSIS OF CASES

As a rule, it is inadvisable and unprofitable to attempt generalization on the basis of a limited number of observations. Yet certain distinguishing features have been sufficiently striking in the records of these eight patients to warrant calling attention to them as aids in defining a distinct clinical group. An analytic summary is given in the accompanying table.

All of these patients were under 50 years of age, two being in the thirty-seventh year. There were seven men and one woman. Five gave a family history of heart disease terminating in sudden death. In five cases, a history of cardiac signs or symptoms preceded the onset of acute coronary obstruction, pain on effort in two, hypertension in two and a heart murmur following a streptococcus infection in one.

In reviewing the histories, the frequency of previous infection commands attention. Cholera, recurring sinusitis, streptococcus sore throat, renal infections with operation, pneumonia and empyema, rheumatic fever and colitis were among the former illnesses noted. The relationship of previous infection to vascular degeneration and thrombosis is unproved, the facts are here recorded without an attempt at explanation. It should be added that in none of the patients was syphilis present, according to the history, clinical examination or serologic test.

Six of the eight patients used tobacco to excess. The seven men were all engaged in activities calling for driving force and worked under pressure, the woman, aged 37, was high-strung, the mother of three children, and an expert horsewoman, and was engaged in directing an amateur theatrical enterprise.

The symptoms of the attack were varied, but no more so than in the more severe types of acute coronary obstruction. As Libman⁶ has stressed, the sensitiveness of the individual to painful stimuli determines, in a measure, the intensity of suffering. Substernal pain was the most common complaint, having been described by five patients. Vomiting accompanied the attack only three times. In case 1, sudden sharp pain in the left arm was the symptom of onset.

Cardiac enlargement was present at the time of the attack in five cases, affording evidence of preexisting cardiac disease. Irregularity of the heart's action, in the form of isolated premature beats, was observed but once, in contradistinction to the relatively greater frequency with which arrhythmias are encountered in the severer forms of coronary occlusion. A fall in blood pressure was noted, however, in all the cases in which determinations were made during and immediately

⁶ Libman, E. Observations on Sensitiveness to Pain, *Tr. A. Am. Physicians* 41: 305, 1926.

following the attack. Fever likewise was present, when looked for, although it was not high, in one instance the rectal temperature rose only to 100 F for twenty-four hours on the day following the onset. In two of the three cases in which blood counts were made, slight leukocytosis (12,000 and 15,000 per cubic millimeter) was found. In a third patient, the leukocytes numbered 9,500, of which 86 per cent were polymorphonuclears.

Changes in the form of the electrocardiogram were recorded in six of the eight cases. As shown in the curves, inversion of the T wave was of the T_1 type,⁷ indicating left coronary involvement in three instances, and of the T_3 type, pointing to right coronary involvement in two cases.⁸ Incomplete bundle branch block, denoting more severe cardiac damage and suggesting a larger area of myocardial infarction, was present only once. Prominence of the Q wave in lead III, first described in coronary occlusion by Wilson,⁹ and mentioned also by Parkinson,⁷ Levine⁴ and Pardee¹⁰ as of diagnostic importance, occurred four times. In my experience, this change is seen more frequently in coronary disease than in any other condition, although it must not be considered as etiologically specific. Elevation of the RT interval of slight degree, as the only change present, was seen once.

Of particular significance in characterizing this group of patients was the extraordinarily rapid rate of recovery, as measured by the patient's desire and ability to resume his customary activities, as well as by objective improvement. Even though prostrated by the severity of the symptoms of onset, several of these persons were never truly bedridden, and as can be seen from the accompanying table, considered themselves well in from twelve hours to ten days. In several instances, rest in bed was enforced with difficulty, occasionally, in spite of warning, threatening and pleading on the part of the physician, the patient left his bed and home, to return to work within a few days. Such abrupt termination of convalescence apparently did not result in immediate disaster. In several of the case reports given by Levine⁴ similar rapid rates of recovery are recorded.

7 Parkinson, J, and Bedford, D. E. Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis), *Heart* **14** 195 (Aug.) 1928.

8 Barnes, A. R., and Whitten, M. B. Study of T-Wave Negativity in Predominant Ventricular Strain, *Am Heart J* **5** 14 (Oct.) 1929. Bell, A., and Pardee, H. E. B. Coronary Thrombosis. Report of Two Cases with Electrocardiographic Localization of the Thrombus in the Right or Left Coronary Arteries, *J A M A* **94** 1555 (May 17) 1930.

9 Wilson, W. T. Cardiac Clinic, with Electrocardiographic Demonstrations, *Ann Clin Med* **5** 238 (Sept.) 1926.

10 Pardee, H. E. B. The Significance of an Electrocardiogram with a Large Q wave in Lead 3, *Arch Int Med* **46** 470 (Sept.) 1930.

To date, one of the eight members of this group has died of a second rapidly fatal attack. One patient had a second occlusion one year after the first, another (the woman) has had two later attacks, one after three months, the second after six months. She has made a good recovery each time.

Restoration of function has been complete in two cases. Two of the patients are free from symptoms on restricted activity. Three have symptoms even with carefully regulated lives—two still complain of pain in the heart and one of dyspnea on effort.

COMMENT

It is tempting to speculate as to the reasons for the mild course of these attacks, but in the absence of necropsy data this is hazardous. Is one dealing with thrombotic closure of small twigs? In comparatively youthful persons, is the unaffected coronary circulation adequate to carry on more efficiently and to adapt itself more quickly than in older persons? Is the rate of healing of the infarct more rapid? Certainly the two conspicuous features of these cases are the relative youth of the patients and the surprising speed of clinical recovery. Again, what rôle do inheritance, infections, excessive use of tobacco and rate of living play in selecting the victim? There are indeed still many unsolved problems.

Recognition of these cases is of more than academic interest. It is important that a heart the circulation of which has suddenly become partly obstructed should receive a sufficiently long period of rest to allow healing of the infarct. In my opinion, a minimum of four weeks in bed is, as a rule, desirable, no matter how mild the character of the attack. Some of the patients here reported, however, apparently have made good recoveries with much shorter periods of rest. Only time will determine the firmness of the myocardial scars. Whether certain of these persons who suffer from an attack in the third or fourth decade of life may recover sufficiently to live out their expected span of years without subsequent cardiac disability must be ascertained by following a considerable number of cases for a long time. In this group of eight patients, as has been indicated, one is dead after four and one-half years, and two have had second attacks within a year. Until more is known concerning the factors that predispose to this condition accurate prognosis, both as to liability to recurrence and life expectancy must remain extremely difficult.

SUMMARY

1. A group of eight cases is reported as exemplifying mild forms of coronary thrombosis.

2 The records of these patients appear to define a distinct clinical group characterized chiefly by (1) the relative youth of the patients (all being under 50 years of age), and (2) the rapid rate of recovery, both subjective and objective

3 A critical analysis is made of the various features, and some of these are discussed. Because the clinical picture is at times atypical it is believed that this condition frequently is not recognized

4 Although a rapid rate of recovery tends to indicate a favorable outcome of the immediate attack, accurate prognosis as to the liability to recurrence and life expectancy is extremely difficult

THE STRUCTURE OF THE NORMAL LUNG

A SURFACE STEREOMICROSCOPIC STUDY *

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When the normal lung is studied by means of surface stereomicroscopy¹ it represents quite a different structural picture than that seen in the ordinary paraffin section of the lung. The ordinary section, which at best is a portion of a millimeter in thickness, shows only a flat view of the lung. The reconstruction study of the lung, in which a careful and painstaking effort is made to fill in the gaps between certain distances, leaves to the imagination the explanation of many facts. The method described in this study supplies not only a surface view, but also a third dimensional view so that one may see a magnified stereoscopic view extending at least 1 cm. in depth. Thus one is enabled to see a magnified picture of the lung without distortion.

THE PLEURAL SURFACE

The pleural surface presents a good view of the lung particularly for the study of the organ in the living animal. The surface under normal conditions is thin and transparent, so that one may observe definite changes in the alveoli and the capillaries. The pleural surface of the lung resembles a honeycomb or the surface of a corn cob. It is made up of circular or polygonal subdivisions, each of which sends branches along the wall of the alveolus, and these meet the larger capillary on the opposite side. Thus in the living frog, turtle or alligator one can notice the blood flowing in one direction, when the flow of blood is rapid, it appears much like the wavy motion produced by the wind on a wheat field. When, however, the circulation slows, one can see the blood flowing in one direction and collecting in the larger capillary on the opposite side.

In certain areas on the pleural surface of the lung, the oblique or longitudinal sections of terminal bronchioles can be seen immediately underneath the visceral pleura. Such a terminal bronchiole ends in a larger sacculi, which varies in size according to the size of the bronchiole.

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1 Joannides, M. The Technique of Surface Microscopy of the Lung, Arch. Int. Med., to be published

terminating at such a point. These arrangements of saccules are the sites of various pathologic conditions, such as formation of pleural bullae resulting from increased intrapulmonic pressure. These bullae may rupture and produce an acute pneumothorax. Such an area is also the site of the bronchogenic extension of pulmonary pathology (pneumonia and tuberculosis for example) to the pleural surface and secondarily to the pleural cavity.

The under surface of the pleura presents quite a different picture when the lung is cut in a way to allow a thin layer of lung tissue to remain attached to the pleura. The lung under such conditions is much like that of a frog, which is a single sac, the inner surface of which contains a series of septums so arranged as to resemble, more or less, a honeycomb. On examination of this surface of the lung, the walls of the alveoli are seen to project from the under surface of the pleura. These walls project into the structure of the lung in such a way as to form polygonal sacculations of varying sizes. The openings of these saccules are somewhat narrower than the remainder of the saccule, and present a slightly thicker tissue in addition to the vessel. In the living alligator such openings have been observed to contract in such a way that they practically close the stom.

The examination of a section of a lung representing the deeper structure shows a motley of facts that can be explained only after a careful, painstaking study not only of the bronchial tree and the vessels, but also of the alveoli. In such a section one is likely to see larger bronchioles or vessels cut transversely, obliquely or longitudinally. Sections of the alveoli at various levels, and of the terminal bronchioles at various angles may also be seen. In order to reconstruct the actual structure of the lung one must study its various parts, and thus eventually one may make up a complete whole which will not be subject to error.

COMPARISON OF THE LUNG TO A SPONGE AND A TREE

For a clearer understanding of the structure of the lung, a comparison between the lung and two well known objects, namely, the common sponge and the tree, is helpful. A gross view of the sponge presents a combination of large and small openings with threadlike tissue between the large ones. If one looks on these large openings or canals as representing the bronchi, one may get a fairly accurate structural comparison between these two organs. The canals in the sponge are so constructed as to allow a maximum amount of water to enter the canals and the smaller subdivisions so that the sponge may absorb oxygen and food from the water. In the lung the bronchi are so constructed as to allow a maximum amount of air to come in contact with the capillaries of the alveoli so that an exchange of gasses may

be accomplished. Because the sponge is an aquatic animal and has to obtain its oxygen from the water, provisions have been made to allow the water actually to come in contact with the smaller subdivisions of the sponge, which under the microscope appear as a dense network of threadlike tissue. In the lung in which air is the means of oxygenation, a somewhat different arrangement is present which allows the air to reach these smaller subdivisions. This has been accomplished by the establishment of a tubular system represented by the bronchial tree. Thus the air is sucked or blown into the smaller subdivisions of the lung. A further provision has been made in the alveoli for allowing this air to reach the smallest capillaries. This is accomplished by the thin wall that is found between these larger capillaries, so that instead of the dense network of threadlike structures that are seen in the sponge one now sees small chambers produced by a thin layer of tissue between



Left

Right

Stereophotomicrograph of the normal human lung expanded to its normal volume and then dried, magnification, $\times 12$. To obtain a clear view, adjust the stereoscope until only one picture is visible and after getting the proper focal distance, keep looking until the stereoscopic view is obtained.

these threads. Such a striking functional and anatomic similarity can be seen in the sponge and the stereomicroscopic picture of the lung that one can safely visualize the lung as a sponge, thus making the picture clearer and easier to grasp.

Another striking comparison that may simplify the conception of the structure of the lung is that between the lung and the tree. The tree is so constructed in its branchings as to give a maximum leaf surface. The lung on the other hand, is so constructed as to give a maximum alveolar surface. One may therefore see a definite similarity in the ultimate distribution of the branchings in the bronchial tree and an ordinary tree. This comparison will help one primarily in visualizing

the mode of branching in the bronchi, since the saccules of air are distributed much in the same manner as are the leaves on an ordinary shade tree

THE BRONCHIAL TREE

The bronchial tree divides from its origin at the trachea in a rather uniform manner. A large bronchus is given off to supply each lobe of the lung. This in turn subdivides into smaller bronchi, which in turn subdivide into tertiary bronchi. There is a tendency toward branching in an acute angle, but there is no regular tendency to dichotomy. The terminal bronchioles arise from the tertiary or quaternary subdivisions. In other words, one does not see any minute subdivisions of the bronchial tree arising from the larger bronchi. Apparently the larger bronchi have two functions, namely, to give rise to smaller bronchi and also to add to the structural strength of the lung. The bronchioles of the third and fourth order are constructed to fill all possible space, but not to support appreciably the general structure. These subdivisions do not have any cartilages and are made up of fairly thin walls. They have an enormous number of terminal bronchioles that are arranged to fill in all available space. Such a branching if seen under the microscope would appear much like the cluster of saccules that fill the space between the larger bronchi and vessels. It might be mentioned in passing that the alveolar tissue immediately surrounding a larger bronchus may arise from the branchings of an adjacent bronchus and have no functional relationship to its neighbor.

The terminal bronchioles as studied by our method show many important facts. These bronchioles are made up of very thin walls, which are so arranged that they present a series of groovelike depressions all along the inner surface of the bronchiole. They terminate in the alveoli which are represented as terminal saccules grouped together at the end of each terminal bronchiole. When a cross-section of such a bronchiole is studied, one is impressed with the appearance of a thin, threadlike structure much like a balustrade in a circular staircase. The grooves that are present along the side opposite this balustrade may be terminal or may branch out into alveoli.

THE NORMAL ALVEOLI

The general appearance of the alveoli is not uniform, and one may see alveoli of various sizes and shapes. Frequently one sees openings in the interalveolar wall connecting two adjacent alveoli. The interalveolar wall is made up of thin, transparent tissue, so that one may see through it from one alveolus to another. An alveolus may be described as a saccul of an irregular shape, either circular or polygonal, with its

walls so arranged as to represent a thin layer of tissue extended between networks of neighboring capillaries, and to allow a given amount of air to remain in this sacculæ as long as possible

When an alveolus is magnified 336 times one gets the impression that the lung is primarily a vascular organ, because the larger capillaries make up the skeleton of the alveolus, and between three or four such capillary stems there is a very thin wall like cigaret paper connecting these stems. This wall is also filled with numerous one-cell capillaries extending all along the surface. The wall of these minute capillaries is so thin that it is invisible, and frequently one gets the impression that the alveolar wall is made up of ridges separated by grooves, the latter representing the pathway of the blood cells. This is quite noticeable particularly in the living frog, in which the blood, after leaving the larger capillary, suddenly runs into a large number of channels in such a way that it appears that the blood is sprayed into an open space and again collects in a larger capillary on the opposite side.

THE MECHANISM OF PNEUMONIA

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The normal lung as seen by surface stereomicroscopy ¹ is made up of a series of saccules separated from one another by a thin, transparent, interalveolar wall. The bulk of this wall is composed of large and small capillaries so arranged as to allow for the largest possible exposure of blood to the alveolar gases. Under normal conditions air enters the alveoli through the terminal bronchiole, and with each expiration a part or the whole of this air is expelled back into the bronchial tree and thence outward.

When inflammation occurs in the alveoli, it has its origin in the vascular tree, in the inner wall of the alveolus or, by extension, in the pleural surface. Regardless of origin the steps of inflammation in the alveolus are practically the same as those in inflammation in any other part of the body. In other words, one would expect hyperemia followed by swelling and exudation and finally resolution or suppuration.

Because of the peculiar saccular structure of the alveoli and the marked vascularity of the organ the lung in undergoing the steps in inflammation presents certain unusual features. Following an irritation to the alveolar lining, one would expect a swelling of the cells and hyperemia in the vessels. With the collection of increased fluid content in the interalveolar wall, the fluids would naturally find their way in the direction of least resistance. The exudate, therefore, would flow into the alveoli, which are filled only with air that can be readily displaced by any fluid. Thus the development of the consolidation of the lung is completed. During the earlier stages of inflammation when a large amount of blood is present in the capillaries of the inflamed area, the exudate is bloody, and it imparts to the lung the appearance of red hepatization. Since the air spaces are filled with liquids, there is no longer crepitation in the tissues, and there is a corresponding absence of the normal resonance imparted by the presence of air in the substance

¹ Submitted for publication, July 21, 1930

From the Department of Surgery, College of Medicine, University of Illinois, Chicago

¹ Joannides M. The Structure of the Lung. A Surface Stereomicroscopic Study. This issue, p 19

of the lung As the inflammatory changes produce a diminution of the red blood elements and an increase of the white blood elements, the color of the exudate changes accordingly from red to gray hepatization

Consolidation of the lung tissue may also occur by the complete occlusion of air in the bronchial tree In such a case the mechanism of fluid exudation depends on the inability of the lung to expand and contract, and thus the fluid elements in the interalveolar wall are dammed back and naturally run into the alveolar sac, filling it up more and more and compressing the air present into a minimal volume In the presence of infection such an area makes a good culture medium for bacteria, and thus gives rise to inflammation ²

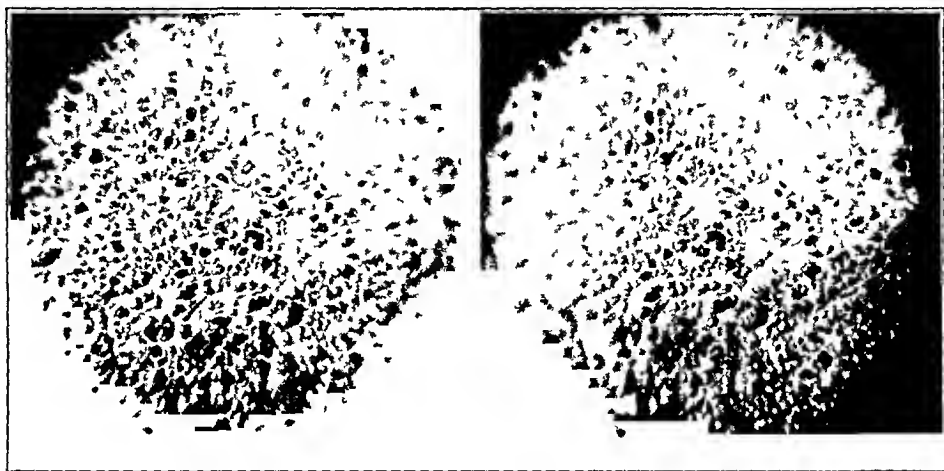
Consolidation may also be developed by introducing fluids into the lung from the outside by means of intrabronchial injection To produce such conditions, the defensive mechanisms of the lung must have been abolished Thus it is quite difficult to introduce small amounts of fluid into the lung when the swallowing and cough reflexes are still present When a large amount of such fluid is injected intrabronchially these reflexes have no protective power When, however, only small quantities (from 10 to 50 cc) are injected, the lung can expel such fluid fairly well, unless it happens to be freshly coagulating blood, which, on reaching the complicated interstices of the alveolar structure, throws its fibrin network in all directions and gets so firm a hold that even the hardest cough cannot expel the blood If fresh or freshly coagulating blood is injected with fusospirochetes, fusospirochete pneumonia and pulmonary abscess may result in a large percentage of cases ³

Compression of the lung produced by pneumothorax, extrapleural thoracoplasty or diaphragmatic hernia does not produce the consolidation seen in inflammatory lesions of the lung It is true that there is less aeration and a very slow gradual fibrosis secondary to the immobilization of the lung in these cases Under such conditions the alveoli are not drowned by exudate, nor is there an inflammatory reaction other than the preexisting one The interalveolar wall retains most of its elasticity, and as soon as the compression is removed, it can again easily expand to its original volume Such has been our experience in the experimental production of diaphragmatic hernia in dogs In these animals a diaphragmatic hernia was produced on the left side, and the dogs were allowed to live from one week to six months At autopsy the cavity of the chest was found to be filled with the gastro-intestinal

² Coryllos, P. N., and Birnbaum, G. L. Obstructive Massive Atelectasis of the Lung, *Arch Surg* **16** 501 (Feb) 1928

³ Joannides, M. The Etiology of Pulmonary Abscess, *Surg Gynec Obst* **47** 449 (Oct) 1928 Hedblom, C. A., Joannides, M., and Rosenthal, S. Pulmonary Abscess An Experimental Study, *Ann Surg* **88** 823 (Nov) 1928

tract, and the lung appeared as a mere appendage of the primary bronchus. On microscopic examination the lung showed the alveoli to be greatly contracted, but they contained air and showed no exudation in the alveolar sac. The interalveolar wall was thicker than normal and presented linear strands just as if numerous threads had been bunched together. This picture has also been observed by surface stereomicroscopy in the clinical examination of patients with lung compression caused by tumors of the bronchi extending into the lung tissue and also in cases of lung compression caused by thoracoplasty, pneumothorax and empyema. In experimental compression of the lung resulting from the production of diaphragmatic hernia, the normal serous membrane of the gastro-intestinal tract came in contact with the serous surface of the pleura, thus avoiding the complications arising from



Surface stereophotomicrograph of a portion of the lung showing stages in pneumonia. Note at the upper right hand corner the edema of the thin alveolar wall, which is not very transparent. At the upper left hand corner the alveolar wall is more edematous, but the alveoli are not obliterated as they are in the center and in the lower half of the picture note the greater thickening of the interalveolar wall. (To obtain a clear view, adjust the stereoscope until only one picture is visible, and after getting the proper focal distance keep looking until the stereoscopic view is obtained.)

irritation of the pleura. Under such conditions the lung could be expanded by increasing the interalveolar pressure, and as soon as it was allowed to expand, practically all traces of compression disappeared, and the alveoli retained their normal contour. A similar expansion of the lung occurs in pneumonia when the intrabronchial pressure is increased to 20 or 35 mm of mercury. A detailed report of these observations will be found in another paper.⁴

⁴ Joannides, M. The Insufflation Treatment for Pneumonia, to be published in the February issue of the Archives of Internal Medicine.

Pneumonia, therefore, may be regarded, microscopically, as a drowning of the alveoli with endogenous or exogenous fluids. This drowning results in the obliteration of the alveolar sacculations giving rise to atelectasis. The interalveolar wall undergoing the changes due to inflammation becomes thicker and less elastic, so that one can see by surface stereomicroscopy (see the accompanying figure) partially or completely occluded alveoli with their walls thickened to many times their original dimensions. As the inflammatory reaction of the lung subsides and the walls get closer and closer to their original thickness, the lung regains its normal elasticity so that it again expands and contracts. The fluids in the alveolar wall then become absorbed as the lung begins again to expand and contract. The exudate in the alveolar sac is coughed up, and the pneumonia reaches its stage of resolution. In the case of pneumonia of the fusospirochete type, the process goes on to destruction with a resultant formation of abscesses.

ERYTHEMA INFECTIONOSUM

A CLINICAL STUDY OF AN EPIDEMIC IN BRANFORD CONN.

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This is a report of ninety-seven cases of erythema infectiosum which occurred in Branford, Conn., during the late fall and winter of 1929-1930. We saw fifty-seven cases in the series and kept clinical records. Information concerning the remainder of the cases was obtained from Dr. A. S. McQueen, health officer, or from the Visiting Nurse Association.

REVIEW OF THE LITERATURE

In 1886, Tschamer¹ reported from Graz an epidemic of thirty cases of an eruptive disease which he differentiated from typical rubella, but considered a modified form (*ortliche rotheln*). Gumplowicz,² in 1891, and Tobieitz,³ in 1898, both from Graz, reported further cases confirming Tschamer's observations and also agreeing with him that the condition was modified German measles. Escherich,⁴ in a discussion of Tobieitz' paper read at Moscow in 1896, was the first to suggest that the disease was a distinct entity. Schmidt,⁵ in 1899, from Escherich's clinic in Graz, described two further epidemics in 1897 and 1899. Escherich⁶ stated that Sticker,⁷ in 1899, described an epidemic in Gies-

¹ Submitted for publication June 24, 1930.

From the Department of Internal Medicine, Yale University School of Medicine.

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1 Tschamer, A. Ueber örtliche Rotheln, *Jahrb. f. Kinderh.* **29** 372, 1889.

2 Gumplowicz, L. Casuistisches und historisches über Rotheln, *Jahrb. f. Kinderh.* **32** 266, 1891.

3 Tobieitz, A. Zur Polymorphie und differential Diagnose der Rubeola, *Arch. f. Kinderh.* **25** 17, 1898.

4 Escherich, T. Tr. Eleventh Internat. Med. Cong. Moscow, 1896, cited by Shaw, H. L. K. *Am. J. M. Sc.* **129** 16, 1905.

5 Schmidt, A. Ueber Rotheln und Erythemepidemien, *Wien. klin. Wchnschr.* **12** 1169, 1899.

6 Escherich, T. Erythema infectiosum, ein neues akutes Exanthem, *Monatsschr. f. Kinderh.* **3** 285, 1904; Demonstration zweier Fälle von Erythema contagiosum, *Wien. klin. Wchnschr.* **17** 631, 1904.

7 Sticker, G. Die neue Kinderseuche in der Umgebung von Giessen (Erythema infectiosum). *Ztschr. f. prakt. Aerzte* **40** 121, 1899, cited by Escherich (footnote 6), cited by Shaw, H. L. K. *Am. J. M. Sc.* **129** 16, 1905, cited by Tobler, L. *Ergebn. d. inn. Med. u. Kinderh.* **14** 70, 1915.

sen, without knowing of the work from Giaz, and gave to the disease the name 'erythema infectiosum,' which was accepted by Escherich. A further description of forty-five cases was given by Berberich,⁸ one of Sticker's students. Other reports have been published by Triple⁹ in 1901 (seventy cases), Feilchenfeld¹⁰ in 1902, Plachte¹¹ in 1904, Heilmann¹² in 1904 (ten cases), Pospischill¹³ in 1904, Escherich¹⁴ in 1904, von Michalowicz¹⁴ in 1910, Heisler¹⁵ in 1914 (twenty-five cases), Tobler¹⁶ in 1914-1915 (sixty-six cases), Weber¹⁷ in 1916, Ochsenius¹⁸ in 1917 (twelve cases), and Kissinger¹⁹ in 1928 (ten cases).

The earliest account of erythema infectiosum published in America was that of Shaw²⁰ in 1905, in which he described cases seen by him in Vienna in 1904 and gave a historical review and clinical discussion. Prior to Shaw's article, descriptions of erythema infectiosum were confined to the German literature, but since 1905 scattered reports have appeared from other countries. In America there have been only a few epidemics reported. Shaw²¹ cited a personal communication from

8 Berberich, E. Eine Epidemie von akutem Erythem bei Kindern (Erythema infectiosum acutum), Diss. Giessen, 1900, cited by Shaw, H. L. K. Am J M Sc **129** 16, 1905.

9 Triple. Erythema infectiosum febrile oder epidemischer Kinderrothlauf, Kalender f. Frauen- und Kinderärzte, Kreuznach, 1901, cited by Shaw, H. L. K. Am J M Sc **129** 16, 1905.

10 Feilchenfeld, L. Erythema simplex marginatum, Deutsche med. Wchnschr. **28** 596, 1902.

11 Plachte. Das Megalerythema epidemicum. Die Grossflecken (Erythema infectiosum Sticker), ein akutes Kinderevanthem, Berl. klin. Wchnschr. **41** 223, 1904.

12 Heilmann, A. Erythema infectiosum, Jahrb. f. Kinderh. **60** 421, 1904.

13 Pospischill, D. Ein neues, als selbständig erkanntes, akutes Exanthem. Wien. klin. Wchnschr. **17** 181 and 701, 1904.

14 von Michalowicz, M. Eine Epidemie des Erythema infectiosum multiforme nach Masern, Jahrb. f. Kinderh. **71** 235, 1910.

15 Heisler, A. Erythema infectiosum, München. med. Wchnschr. **61** 1684, 1914.

16 Tobler, L. Zur Breslauer Epidemie von Erythema infectiosum, Berl. klin. Wchnschr. **51** 544, 1914, Erythema infectiosum, Ergebn. d. inn. Med. u. Kinderh. **14** 70, 1915.

17 Weber, J. Das Erythema infectiosum, Cor.-Bl. f. Schweiz. Aerzte **46** 1453, 1916.

18 Ochsenius, K. Ueber Erythema infectiosum, München. med. Wchnschr. **64** 838, 1917.

19 Kissinger, P. Zehn Fälle von Erythema infectiosum, München. med. Wchnschr. **75** 1381, 1928.

20 Shaw, H. L. K. Erythema Infectiosum, Am J M Sc **129** 16, 1905.

21 Shaw, H. L. K. Erythema Infectiosum, Nelson's Loose-Leaf Living Medicine, New York, T. Nelson & Sons, 1920, vol. 1, p. 911, Erythema Infectiosum, in Abt, I. A. Pediatrics, Philadelphia, W. B. Saunders Company, 1924, vol. 5, p. 660.

Dr Bianer of Hamburg, New York, concerning a local epidemic of thirty-seven cases occurring in the spring of 1919 Zahorsky,²² in 1924, reported nine cases from St Louis and mentioned having had several cases during a local epidemic about ten years previously In 1926, Herrick²³ published a clinical report of seventy-four cases personally observed during 1924 and 1925 in Cleveland Heights Feeley,²⁴ in 1928, reported one case which he diagnosed erythema infectiosum Smith,²⁵ in 1929, reported fourteen cases from Ogden, Utah, occurring in the fall of 1927 and the spring of 1928

In 1926, Hanneman²⁶ reported an epidemic from the Netherlands, in 1927, Taccone²⁷ reported one from Milan In 1928, Cathala and Cambessédès²⁸ reported cases in five of seven children in one family Halle, in a discussion on their paper, mentioned having seen a small epidemic in a private school three years before the World War

The descriptions of the disease as given by the various authors are essentially in agreement Several different names have been applied to the condition örtliche Rotheln, megalerythema epidemicum, exanthema variable, erythema simplex marginatum, erythema infantum febrile, epidemische kindermotlauf and fifth disease, but, at the present time, erythema infectiosum seems to be generally accepted

Complete discussions of erythema infectiosum are given by Tobler,²⁹ Stooss³⁰ and Shaw³¹ The following account is summarized from Shaw He defined erythema infectiosum as a feebly contagious disease occurring chiefly in children, with very slight subjective symptoms characterized by a maculopapular rose-red rash more pronounced on the cheeks, legs and outer surface of the arms Nothing is known as to the etiology He stated that in cases in which it was possible to make

22 Zahorsky, J An Epidemic of Erythema Infectiosum, *Am J Dis Child* **28** 261 (Aug) 1924

23 Herrick, T P Erythema Infectiosum A Clinical Report of Seventy-Four Cases, *Am J Dis Child* **31** 486 (April) 1926

24 Feeley, J B Erythema Infectiosum, *Atlantic M J* **31** 752, 1928

25 Smith, E H An Epidemic of Erythema Infectiosum "The Fifth Disease," *Arch Pediat* **46** 456, 1929

26 Hanneman, Y Incubation Time of Infectious Erythema, *Nederl tijdschr v geneesk* **70** 1984, 1926, abstr, *J A M A* **88** 138 (Jan 8) 1927

27 Taccone, G Un' epidemia di "quinta malattia" (eritemo infettivo), *Riv di clin pediat* **25** 145, 1927, abstr, *J A M A* **88** 2005 (June 18) 1927

28 Cathalá, J, and Cambessedes, H Note sur une epidemie familiale d'erytheme infectieux paraissent devoir être rattachée a la "cinquieme maladie," *Bull et mem Soc med d hôp de Paris* **52** 205, 1928

29 Tobler (footnote 16, first reference)

30 Stooss, M Erythema infectiosum (Megalerythem), in Pfaundler and Schlossmann *Handbuch der Kinderheilkunde*, ed 3, Leipzig F C W Vogel, 1923, vol 2, p 235

31 Shaw (footnotes 20 and 21)

correct observations, the period of incubation was from six to fourteen days. The most characteristic feature of the disease is the eruption, which often is the first and only symptom, although there may be a prodromal stage with slight malaise and sore throat. The rash appears first on the face, and is there quite characteristic. The cheeks are chiefly involved, with a confluent eruption resembling erysipelas in appearance. The skin over the cheeks has a rose-red efflorescence, is swollen, is hot to the touch, but not sensitive to itching, and is usually separated from the normal skin by a well defined, slightly raised edge, although the two may merge gradually. The nasolabial region is not involved while discrete spots may be seen on the forehead and chin. The rash, which is symmetrical, spreads peripherally, appearing on the body and extrem-



Fig 1 (case 81) —Fourth day. Upper arm and trunk, showing the typical appearance of the rash.

ities about the second day. It is most marked on the extensor surfaces of the arms and legs and on the buttocks, the trunk invariably being less involved than the face and the extremities. The eruption is typical and characteristic on the extremities. Maculopapular spots appear which fade from the center leaving a lacelike or geographic appearance. This is well shown in figure 1 from case 81. The rash is more macular than papular, with only a slight elevation except on the face, and it blanches momentarily on pressure. It is not seen in the mouth or fauces. A peculiar evanescence is often noted. The rash apparently disappears, but reappears after slight irritation of the skin. The eruption fades rapidly from the face and trunk, but may last on the extremities from six to ten days. There is no desquamation, staining or marking. Shaw states that the subjective symptoms are conspicuous by

their absence, although a few adults have complained of a burning and pulling sensation in the cheeks and also of some joint tenderness. There is no coryza or cough, the conjunctivae are not congested, the lymph nodes are not enlarged and the urine is normal. The tongue may be slightly coated, and there may be slight fever. There are no complications or sequelae, and no treatment is recommended.

CLINICAL OBSERVATIONS

Table 1 gives the sex, age, date of onset, duration of rash, previous cases in the family and school attended in the ninety-seven cases of the epidemic in Branford, as far as such information could be obtained. The cases that we have seen are starred. There were fifty-four females and forty-three males. Eighty-eight of the ninety-seven patients were from 4 to 12 years of age, with an average in that age group of $8\frac{1}{2}$ years. The youngest patient was 8 months old, the oldest 45 years. The duration of the rash varied from two to twenty-four days. In Henrick's ²³ cases the duration was from three to twenty-one days.

The following description is based on our series of fifty-seven cases. There were no definite prodromal symptoms. Twelve children gave a history of a mild upper respiratory infection within one week before the appearance of the rash, which may have been incidental, as many of them were known to be subject to frequent colds. In three children colds developed after the rash was full blown. Five children had questionable slight malaise for from one to two days preceding the appearance of the rash. In all other instances the rash was the first symptom noted and was the only symptom in the majority of cases. In most of the cases, the rash appeared first on the face. When it was well developed, the cheeks were fiery red and the patient appeared overheated. The rose-red efflorescence mentioned by many authors was particularly well marked in brunettes. On close inspection the rash was seen to consist of rose-red maculopapules which became confluent over the cheeks but might remain discrete or produce a gyrate pattern as it extended back toward the ears. The patterned rash sometimes extended across the angle of the jaw and along the neck below the ear and, rarely, back of the ear. It was at times seen on the chin or forehead, or there might be discrete spots in these areas. The color here was never so brilliant as over the cheeks. The rash usually did not bridge the nose but sometimes extended onto the sides. The confluent area felt hot to the touch and had a slightly elevated edge. There was a definite circumoral pallor. In no case was the rash seen to extend beyond the nasolabial folds. The rash on the face lasted from one to three or four days, rarely longer.

TABLE 1—Cases of Erythema Infectiosum

Case	Age	Sex	Previous Cases in Family	Date of Onset	Duration in Days	School
1 M Z	8	F	None	Nov 2	10	Center 3
2 M E	6	F	None	Nov 6	3	Harrison A 1
3 M M	11	F	None	Nov 9	9	Laurel St 7
*4 J W	11	F	None	Nov 10	11	Laurel St 7
5 A R	6	F	None	Nov 11	21	Harbor St 1
*6 H R	4	F	None	Nov 11	10	
7 A S	6	M	None	Nov 12	3	Harrison A 1
8 H D	8	F	None	Nov 12	17	Center 3
9 J D	10	M	None	Nov 12	6	Center 5
10 R D	7	M	None	Nov 13	5	Center 2
*11 M P	11	F	None	Nov 13	8	Center 6
*12 B F	9	F	None	Nov 13	15	Center 5
*13 S R	9	F	Case 5	Nov 13	15	Harbor St 4
14 B S	9	F	None	Nov 13	5	Center 4
15 M B	6	F	None	Nov 14	3	Harrison A 1
16 N P	9	M	None	Nov 14	9	Center 4
*17 F R	11	F	Cases 5, 13	Nov 15	11	Harbor St 6
*18 K G	3	F	None	Nov 15	14	
*19 G B	10	M	None	Nov 15	6	Center 4
20 A S	11	F	None	Nov 16	3	Center 6
*21 M Z	45	F	Case 1	Nov 17	7	
*22 T K	6	M	None	Nov 18	7	Harbor St 1
*23 M M	7	M	None	Nov 18	10	Canoebrook 2
24 L A	11	F	None	Nov 18	3	Center 4
*25 M D	10	F	Case 9	Nov 19	10	Center 5
*26 R O	8	M	None	Nov 20	21	Center 3
*27 A B	8	F	None	Nov 20	11	Center 3
*28 C B	11	M	Case 19	Nov 20		Center 6
*29 O B	10	M	None	Nov 20	5	Center 5
*30 A M	9	M	None	Nov 21	14	Harbor St 3
31 G D	6	M	Case 8	Nov 22	9	Harrison A 1
*32 G F	8	M	None	Nov 22	13	Center 4
*33 J C	7	M	None	Nov 22	14	Harbor St 3
*34 F P	12	M	Case 11	Nov 23	17	Center 6
*35 M D	2	F	None	Nov 24	8	
*36 E B	12	F	None	Nov 24	6	Laurel St 7
37 E J	8	F	None	Nov 24		Center 3
*38 D B	6	F	?	Nov 25	7	Harrison A 1
*39 A A	8	M	None	Nov 25	14	Center 3
*40 C A	9	F	Case 24	Nov 25	24	Center 3
*41 M P	11	F	Case 16	Nov 25	15	Center 6
*42 A W	8	F	None	Nov 25		Center 3
*43 V A	8	F	None	Nov 25	12	Center 3
*44 M M	8	F	None	Nov 25	12	Center 3
*45 E H	8	F	Case 39	Nov 27	8	Center 3
46 M B	5	F	None	Nov 27	2	Har Av Kind
*47 O K	9	F	None	Nov 28	14	Center 3
*48 T O	9	M	None	Nov 28	12	Center 3
*49 S K	8	M	None	Dec 2	14	Center 3
*50 B P	11	F	None	Dec 4	16	Center 6
*51 V P	10	F	None	Dec 4	4	Indian Neck 5
*52 L A	9	F	None	Dec 5	7	Center 3
*53 M O	8	F	None	Dec 5	11	Center 2
*54 V A	8	M	None	Dec 5	13	Center 2
*55 J B	12	F	None	Dec 6	15	Center 6
*56 G B	10	M	Case 46	Dec 6	5	Center 5
57 D J	5	F	None	Dec 8		
*58 A P	10	F	Cases 11, 34	Dec 10	7	Center 5
*59 J P	8	F	Cases 11, 34	Dec 10	8	Center 3
60 H J	7	M	Case 57	Dec 11		Harrison A 2
*61 G D	9	F	?	Dec 13	10	Center 4
*62 R B	5	M	None	Dec 14	14	
*63 N W	9	F	None	Dec 14	10	Center 4
*64 M B	9	M	Case 62	Dec 15	10	Canoebrook 4
65 H L	11	F	None	Dec 17		Harbor St 5
*66 R J	12	M	Cases 57, 60	Dec 17	7	Center 5
67 I P	5	F	Cases 11, 34, 58, 59	Dec 18	7	
*68 F B	7	M	None	Dec 18	6	Harrison A 2
69 J S	12	M	None	Dec 18		Laurel St 8
70 G H	8	F	None	Dec 26		Stony Creek 2
71 A P	7	M	Cases 11, 34, 58, 59, 67	Dec 28	7	Center 2
72 E H	10	F	Case 70	Jan 1		Stony Creek 6
*73 H D	7	M	None	Jan 2	14	Indian Neck 2
*74 J C	8	M	None	Jan 2	14	Indian Neck 3
*75 A T	6	F	None	Jan 2		Canoebrook 1
*76 K O	6	M	None	Jan 2		Indian Neck 1
77 H B	33	I	None	Jan 2	2	
78 S O	20	F	None	Jan 2		
79 G D	4	F	Case 73	Jan 5	21	
*80 H H	8	M	None	Jan 7	5	Center 3
*81 R D	8	M	Cases 73, 79	Jan 8	18	Indian Neck 3
82 H M	9	F	None	Jan 9	6	Harbor St 3
*83 J W	8 mo	M	None	Jan 11	21	

* Cases seen by authors

TABLE 1—*Cases of Erythema Infectiosum—Continued*

Case	Age	Sex	Previous Cases in Family	Date of Onset	Duration in Days	School
*84 S W	35	M	Case 83	Jan 13	24	
85 D C	14	M	None	Jan 15		Laurel St 8
*86 T W	12	M	Cases 83, 84	Jan 17	5	Laurel St 8
87 P D	12	F	None	Jan 17		Laurel St 8
88 A R	10	M	None	Jan 17		Canoebrook 4
89 W L	12	M	None	Jan 21		Harbor 5
*90 L M	11	F	Case 25	Jan 22	8	Canoebrook 6
91 P L	8	M	Case 89	Jan 23		Harbor 2
92 R V	10	M	Cases 83, 84, 86	Jan 27	7	Center 5
93 A B	13	M	None	Jan 29		Laurel 8
94 D S	10	M	None	Feb 3		Center 3
95 M H	10	M	None	Feb 4		Indian Neck 4
96 H M	9	F	None	Feb 5		Canoebrook 1
97 R H	8	F	None	Feb 19		Center 3

* Cases seen by authors

About one day after its appearance on the face the patterned rash appeared on the extensor surfaces of the arms, usually appearing first on the upper arms and subsequently on the forearms and dorsal surfaces of the hands (fig 2). Within from twenty-four to forty-eight hours it extended to the flexor surfaces, tending at the same time to clear on the extensor surface, leaving pale areas outlined by the traceries of the rash. Figure 3 shows this clearing, although in this case it occurred somewhat earlier than usual. The legs and trunk were involved at approximately the same time as the arms, or some hours later. The buttocks frequently showed a more brilliant rash than the extremities, usually maculopapular in character. In some cases the trunk showed no eruption, or only a few isolated spots usually over the chest and back. A small number of cases showed a diffuse rash over the trunk. The eruption on the legs resembled that on the arms and was always more marked on the extensor surfaces. Rarely it extended to the dorsal surfaces of the feet. The axillary folds, when involved, the wrists and the elbows showed a more brilliantly colored rash than was observed elsewhere on the extremities. The rash might persist for some time on the wrists and around the elbows after it had disappeared from the rest of the body. A cyanotic mottling of the extremities in the late stage or following the rash was seen in several cases, an appearance which would seem to resemble the marble-like mottling of Braner³² and the dusky mottling like a faint cyanosis described by Herrick²³. Although the rash in general was quite characteristic, it varied somewhat in individual cases. Some patients either had no rash on the face or it was overlooked. Several showed the characteristic patterned rash only on the arms. In some cases the rash was definitely elevated in some

32 Braner, cited by Shaw (footnote 21, second reference)

areas, especially over the upper arm and shoulder, in others it was apparently macular. It faded momentarily on pressure. The evanescence noted by previous writers was observed in many of these cases. There was no desquamation or staining. No eruption was seen in the mouth.

Symptoms and signs other than the rash were few or absent. Three adults complained of burning of the cheeks and itching of the rash.



Fig 2 (case 64) —Second day of rash. Left arm, showing characteristic patterned rash.

Only two children complained of itching. Of sixty-eight temperature readings, four were above 100 F. Two patients had a temperature of 102 F at the onset, the highest reading recorded. The others ranged from normal to 99.8 F. Several patients showed slight conjunctival injection, which disappeared as the rash cleared. Several showed slight injection of the anterior fauces, but none had symptoms of sore throat. Eight patients had herpes labialis. A few children had enlarged, non-tender cervical lymph nodes, but were known to have had them previously. The 2 year old patient was considered by her mother more

TABLE 2—*Leukocyte and Differential Counts*

Case	Age	Sex	Day of Rash	Temper- ature, F	White Blood Cells	Poly- morpho- nuclears	Lym- pho- cytes	Mono- cytes	Eosino- phils	Baso- phils	Un- classi- fied
35	2	F	4 6	99.6(R) 99.6(R)	11,700 13,200	39.40 47.50	41.20 33.25	6.20 9.25	11.60 9.00	0.60 0.25	1.00 0.75
62	5	M	3		9,600	63.00	20.25	8.50	6.50	0.50	1.25
22	6	M	5	99.2	10,200	56.75	31.25	7.00	2.75	0.75	1.50
38	6	F	1 3 8	98.6 99.0 99.7	6,600 5,300 6,300	44.80 48.25 53.00	37.00 36.50 33.75	9.40 9.25 7.50	7.40 5.75 3.75	1.20 0.25 0.50	0.20 0.00 1.50
68	7	M	1 3	99.6	7,600 5,500						
26	8	M	3 6 8 10 13 16 20	99.2 99.0 99.6 99.6 99.4 99.2 97.8	6,900 7,000 6,700 8,100 6,100 7,500 6,300	48.99 49.00 46.75 57.25 54.50 54.50 46.50	38.33 39.50 42.25 31.00 31.25 38.25 40.25	5.62 6.00 5.25 7.25 8.65 3.25 7.75	4.68 3.00 2.50 2.50 3.10 1.75 3.25	0.96 1.25 1.00 2.00 1.00 0.50 0.50	1.37 1.25 1.25 0.00 1.50 1.75 1.75
28	8	F	5	99.0	8,200	53.75	34.75	7.75	2.25	0.00	1.50
39	8	M	1 3	98.6 98.2	7,800 7,800	59.00 62.25	30.00 28.75	8.00 5.00	2.25 3.25	0.50 0.00	0.25 0.75
32	8	M	6 11	99.5	8,500 7,700	45.50 51.00	42.75 35.20	7.25 6.60	3.75 4.60	0.50 0.60	0.25 2.00
44	8	F	8	99.2	9,100	68.50	19.50	3.75	6.50	0.25	1.50
49	8	M	4 8	99.0 99.1	6,100 7,600	47.50 69.00	35.25 23.25	2.75 2.50	12.75 4.75	0.50 0.25	1.25 0.25
53	8	F	1	99.6	14,400	60.50	32.75	2.50	3.00	0.25	1.00
12	9	F	10		7,600	70.75	18.75	6.25	1.00	1.75	1.50
30	9	M	2 12	99.4	8,200 6,800	46.30 51.00	37.40 34.50	13.16 7.00	2.00 4.50	0.00 0.75	1.58 2.25
13	9	F	1	99.8	6,400	48.50	31.75	9.50	8.50	0.25	1.50
40	9	F	3 8 11	98.8 99.4 98.4	7,400 6,500 7,900	55.75 57.60 46.25	29.75 28.00 41.00	6.75 4.60 3.00	5.75 6.80 8.00	1.25 0.40 0.25	0.75 2.60 1.50
48	9	M	8	99.8	8,600	52.75	31.25	6.75	6.75	0.25	2.25
52	9	F	1	99.8	9,500	66.00	26.25	1.75	4.50	0.00	1.50
61	9	F	4 6	99.1 99.5	6,700 8,000	52.25 52.50	29.75 28.75	4.50 6.75	10.50 10.50	0.50 0.50	2.50 1.00
64	9	M	2 4		7,100 7,100	61.25	27.50	8.25	1.75	0.25	0.75
63	9	F	7	98.8	5,900						
29	10	M	3		7,300	50.25	39.00	4.25	4.25	1.00	1.25
25	10	F	4	99.2	10,800	52.50	38.00	5.50	2.50	0.50	1.00
51	10	F	2	100.2	6,000	57.25	33.50	4.75	2.50	0.50	1.50
11	11	F	5		5,200	39.00	37.00	11.00	13.00	0.00	0.00
41	11	F	11 15	99.0	6,200 6,000	52.25 53.25	37.75 34.75	3.25 5.00	5.50 5.50	0.00 0.50	1.25 1.00
50	11	F	2	99.8	8,000	51.50	40.25	5.50	2.75	0.00	0.00
34	12	M	10 13	99.2	7,000 9,000	50.50 49.50	31.00 40.00	6.50 5.25	10.00 4.00	0.25 0.50	1.75 0.75
36	12	F	4	99.0	8,400	49.50	36.25	5.75	7.50	1.00	0.00
66	12	M	4		5,100						
84	35	M	7		5,800						
6	4	F	7			48.00	30.50	8.00	13.50	0.00	0.00
14	9	F	5			42.50	46.50	7.00	3.50	0.50	0.00
19	10	M	3			56.40	34.80	4.00	3.60	0.20	1.00
4	11	F	8			41.50	49.00	4.50	4.00	1.00	0.00



Fig. 3 (case 64) —Second day of rash. Left arm extensor surface, showing cleared central area which appears as rash extends to flexor surface

irritable than usual. Otherwise no changes were noted in any of the cases. No complications or sequelae were observed.

The results of leukocyte and differential counts are given in table 2. The distribution of leukocyte counts on different days of the rash is shown in figure 4. The counts were all taken by one person. Differential counts were made on paired cover slip preparations, and a minimum of 400 cells counted. The cells included as unclassified were mainly pathologic lymphocytes. The counts show no leukocytosis, but a tendency toward eosinophilia and a relative lymphocytosis. Heilick²³ reported 7 counts which he considered to be of no diagnostic significance.

Cultures taken from the throat in twelve cases and planted on blood agar plates showed only the usual mouth flora.

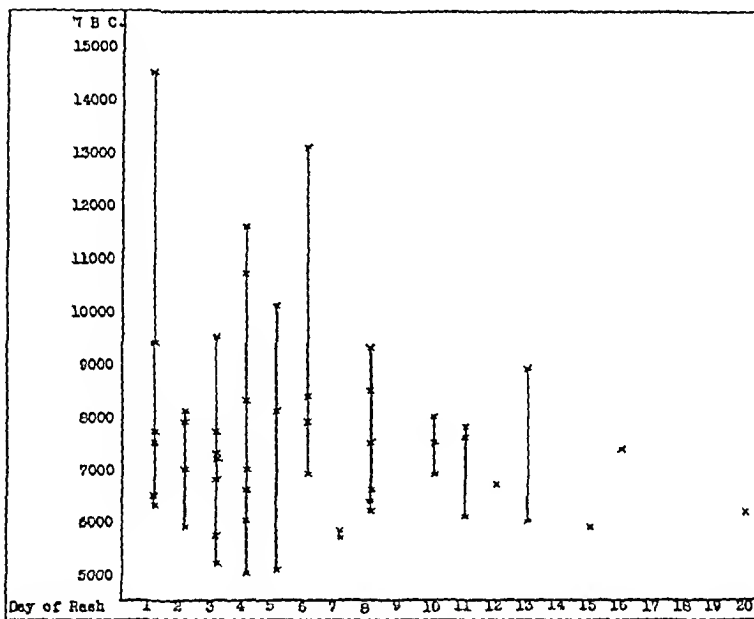


Fig. 4—Leukocyte counts according to the day of the rash.

SELECTED CASE HISTORIES

CASE 25—On November 19, a girl, aged 10 years (brother, case 9, had a rash starting on November 12), was reported by the visiting nurse to have marked rash on the face and body, the temperature was 102 F. There were no prodromal symptoms. We first saw the patient on November 20, at which time the temperature was 99.8 F, the conjunctivae and anterior pillars of the fauces were slightly injected. The face showed a very red efflorescent rash with an erysipeloid distribution and an elevated margin, and was very hot to the touch. There was an extensive, dusky red, maculopapular eruption over the trunk and extremities, the groups of lesions separated by clear spaces giving a blotchy appearance. On November 22, the temperature was 99.2 F, the conjunctivae and anterior fauces were still slightly injected and the rash on the face was fading. On the extensor surfaces of the arms the rash was practically confluent and quite red and extended to the dorsal surfaces of the hands. The flexor surfaces of the arms were mottled and somewhat cyanotic. The rash was marked over the buttocks and lateral aspects of the thighs and slight over the chest and back, with a faint

lacy rash on the abdomen. On November 25, the rash had disappeared from the face, but was still present on the dorsal surfaces of the hands, including the proximal phalanges, and over the extensor surfaces of the elbows. A mottled rash was present over the buttocks. On the tenth day, the rash had entirely disappeared. There were no other symptoms during the period of observation.

CASE 39—A boy, aged 8 years, first noticed a rash on the arms on November 25. We first saw him on the same day. The face appeared flushed but showed no definite eruption. The cervical glands were enlarged, but not tender (adenoid facies). The throat was not injected. There was a patterned rash over the extensor surfaces of the arms, more marked on the upper arm. The chest and buttocks appeared mottled. The temperature was 98.6 F. On November 27, the rash was still present on the extensor surfaces of the arms and on the buttocks, with a marked rash on the anterior surfaces of the thighs. On November 29, there was a slight rash on the flexor surfaces of the forearms. On December 2, a definite marbled rash was present over the thighs, anteriorly and posteriorly. There was no rash elsewhere. All of the rash was gone in two weeks. There were no other symptoms.

CASE 51—On December 4, a girl, aged 10 years, was sent home from school by the visiting nurse because of a brilliant rash on the face. We first saw her on December 5, at which time the temperature was 100.2 F, the conjunctivae were slightly injected, but the throat was not. The cheeks showed a confluent, slightly raised rash, which was hot to the touch. A rash was present on the chin extending onto its under surface. There was a patterned rash on the arms, more marked on the flexor surfaces. The anterior and posterior axillary folds were covered with a brilliant rash. After exposure to the cool air of the room, a definite rash appeared on the chest, abdomen, buttocks and thighs. On December 6, the rash was clearing up, but was still marked on the arms. On the fifth day, the rash had entirely disappeared. There was no recurrence. There were no other symptoms.

EPIDEMIOLOGY

Tobler³³ mentioned the fact that all the available communications on erythema infectiosum report group infections, and that epidemics varying in extent may recur in the same place after intervals of a few years, he cited specifically the reports of Schmidt, Gumpłowicz and Tobnitz from Graz. He does not think that individual reports from a large city give an accurate picture of the actual spread of the disease, and that because of the lack of symptoms and the fact that the disease is not reportable, the actual figures are probably much higher than those reported. His own series of cases from Breslau came almost entirely from the material of a single clinic in a city of more than half a million, while it was estimated that two thirds of the patients came from the neighboring quarters of the city. He expressed the belief that this should be taken into consideration in interpreting the distribution of his cases, the greater number of which occurred in the neighborhood of the clinic. He said that the actual morbidity in Breslau was much greater than that reported by him. He considered that the fact that erythema

33 Tobler (footnote 16, second reference)

infectiosum is frequently reported as occurring in association with one of the following measles, German measles and scarlet fever does not indicate any essential connection. For weeks during the Bieslau epidemic which lasted from November, 1913, to March, 1914, erythema infectiosum was the only observed infectious exanthem.

Shaw³⁴ stated that as the disease is not found frequently it may be assumed that the contagiousness is limited or the predisposition is not general. He mentioned that a number of Weber's cases occurred in an orphan asylum where only two or three cases developed a week. In many instances it has been reported to spread through families. Herrick²³ noted that in the 1925 epidemic in Cleveland Heights there were no cases in the school in which most of the cases were observed.

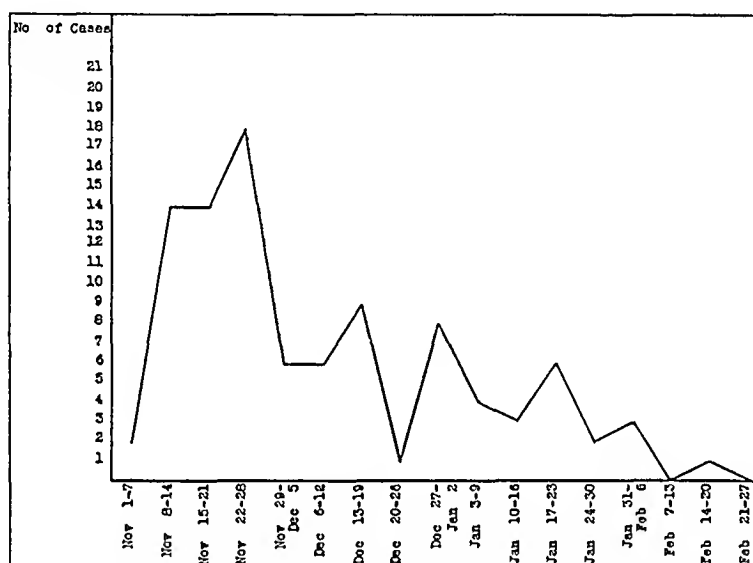


Fig 5—Incidence of reported cases by weeks

during the 1924 epidemic. He considered that one attack establishes a specific immunity.

The present epidemic of erythema infectiosum began on Nov 1, 1929, and lasted until the middle of February, 1930. The number of cases by weeks is given in figure 5.

Analyses of the city water supply, made by the laboratories of the State of Connecticut Department of Health, on Oct 22 and Nov 19, 1929, were reported by Dr I V Hiscock to show nothing abnormal. The water supply of one family, in which cases 62 and 64 occurred, was from a private well. In case 62, that of a preschool child, the patient was stated to have had no water except that from the home well for at least two weeks prior to the appearance of the rash. In case 64, however, the patient attended school, and the first signs of rash devel-

34 Shaw (footnote 21, first reference)

oped one day after its appearance in the patient in case 62. Milk and food supplies were investigated by the local health officer, and were considered to have no epidemiologic significance.

Of sixty-eight families in the series with two or more children, seventeen had more than one case. In one family with six children, all six had erythema infectiosum, the largest number of cases in one family observed in the present series—case 11, onset November 13, case 34,

TABLE 3—*Incidence of Cases in Schools*

School	Room	Enrollment	Cases	Total Enrollment	Total Cases
Center	Grades II and III	31	5	204	45
	Grade III	41	18		
	Grade IV	43	7		
	Grade V	48	8		
	Grade VI	41	7		
Canoebrook	Grade I	32	2	149	6
	Grades II and III	40	1		
	Grades IV and V	39	2		
	Grades V and VI	38	1		
Harbor St	Opportunity	13	0	120	10
	Grades I and II	40	3		
	Grades III and IV	36	4		
	Grades V and VI	31	3		
Harrison Avenue	Kindergarten	48	1	120	8
	Grade I	41	5		
	Grades I and II	31	2		
Indian Neck	Grades I, II, III and IV	44	5	77	6
	Grades V and VI	33	1		
Laurel St	Grade VII-1	21	0	258	8
	Grade VII-2	41	1		
	Grade VII-3	41	2		
	Grade VIII-1	37	1		
	Grade VIII-2	39	0		
	Grade VIII-3	79	4		
Stony Creek	Grades I and II	33	1	175	2
	Grades II and III	37	0		
	Grades IV and V	38	0		
	Grades VI and VII	33	1		
	Grade VIII	34	0		
All schools				1,103	85

November 23, cases 58 and 59, December 10, case 67, December 18, case 71, December 28.

Eighty-five of the cases occurred in school children. It is interesting to note that the first patient attended Center School, in which there were forty-five cases in all, the highest incidence in any of the schools. Cases by schools are given in table 3. The distribution of cases in the town was fairly general, and not confined particularly to any one locality.

In fifty cases information was obtained, from parents in the case of children, with respect to a previous history of measles, rubella and scarlet fever. Forty-one of the fifty patients had had measles, eleven rubella and five scarlet fever, while ten had had both measles and rubella.

and five both measles and scarlet fever. Twenty-six had had measles only and one rubella only, while none of the fifty had had all three. Immediately preceding and during the time of the epidemic, there were no known cases of measles or rubella in the town.

EXPERIMENTAL OBSERVATIONS

Nasopharyngeal washings were obtained from two cases, one on the first day of the rash and one on the eighth day. These washings were made with from 15 to 20 cc of sterile physiologic solution of sodium chloride, kept at body temperature, and each within one hour was inoculated, unfiltered, under aseptic conditions, into a healthy white male rabbit, the abdomen and flanks of which had been shaved from twenty-four to forty-eight hours previously. The inoculations were made intraperitoneally, intratesticularly and on the scarified cornea. Control rabbits, shaved at the same time as the former, were similarly inoculated with sterile physiologic solution of sodium chloride. Daily observations were made, and it was felt that no significant results were obtained. There were no local reactions at the sites of injection and no skin changes, and the rabbits maintained normal appetites and apparently remained well.

SUMMARY

An epidemic of ninety-seven cases of erythema infectiosum occurring in Branford, Conn., is reported. The results of clinical examinations, including reports on leukocyte and differential counts and throat cultures, are given. The epidemiology is discussed, including the incidence of cases in families and schools. Experimental work, the results of which were entirely negative, is cited.

The epidemic in Branford was similar in all respects to previously reported epidemics of erythema infectiosum. The characteristic features of the disease are the rash, its distribution, the evanescence, the relatively long duration and the absence of other symptoms. It seems to be a distinct clinical entity, and all evidence points to its being transmitted from person to person, although the exact mode of transmission and the etiology of the disease are unknown.

LEUKEMIC CHANGES OF THE GASTRO- INTESTINAL TRACT*

W SCLAIR BOIKAN, M D

CHICAGO

In leukemia, the gastro-intestinal tract has received but little attention. Symptoms referable to it are usually interpreted on the basis of the coexistent cachexia and anemia. Roentgen studies are few (Holmes, Dresser and Camp¹), and in most instances the pathologic changes are discovered only at autopsy. Involvement of the gastro-intestinal tract by the leukemic process is not only of theoretical, but also of practical, interest, as gastro-intestinal leukemia may dominate the clinical picture. Even emergency operations may be found necessary when intussusception or perforation occurs.

Fourteen cases of leukemia, eleven myelogenous and three lymphatic, were studied with particular reference to the gastro-intestinal changes. One, a case of chronic lymphatic leukemia, will be presented in detail because of features of great rarity. The remaining cases will be analyzed in the general comment and review of the literature.

REPORT OF A CASE

History—W. W., a white man, aged 50, entered the Cook County Hospital on Feb. 21, 1930. He stated that in the past four months he had noticed that his abdomen was getting larger. He had had no abdominal distress of any kind. Simultaneously, a few nodules had appeared below the jaw on both sides. In the last two months, the swelling had increased so much as to make it difficult for him to open his mouth. In the past two weeks, his gums had become swollen, were painful and prohibited chewing. The teeth were falling out painlessly. Recently his ankles had begun to swell. Further questioning elicited the fact that the patient suffered from a moderate diarrhea of from three to four watery bowel movements per day.

The past history was of no significance.

Examination—On physical examination, he was markedly emaciated. The gums were swollen and tender and discharged pus from the alveoli of the jaw. There was a markedly foul odor from his mouth. The cervical glands formed huge masses, unattached to the skin and moderately adherent to each other, discrete nodules were present in the posterior triangles of the neck. The heart showed no abnormalities.

The lungs were normal, except for a limitation of expansion on the left side.

Submitted for publication, July 14, 1930.

*From the Department of Pathology, Cook County Hospital.

1 Holmes, G. W., Dresser, R., and Camp, J. Lymphoblastoma. Its Gastric Manifestations with Special Reference to the Roentgen Findings, *Radiology* 7 44, 1926.

In the abdomen, the liver was found 5 fingerbreadths below the costal margin. The spleen extended from the fourth rib in the midaxillary line to the costal margin and had a firm, notched edge.

There was a moderate amount of shifting dullness in both flanks. The lower extremities pitted on pressure.

Examination of the blood showed the following: erythrocytes, 2,000,000, hemoglobin, 40 per cent, leukocytes, 86,000, lymphoblasts, 92 per cent, lymphocytes, 4 per cent, neutrophil leukocytes, 3 per cent, nucleated red blood corpuscles, 0, basophils, eosinophils, mononuclears, 0, and platelets, 120,000.

The nucleus of the lymphoblast was trabeculated and moderately dense. The cytoplasm was ample and slightly basophil, with many azurophil granules. The oxydase reaction was negative. The red blood corpuscles showed slight anisocytosis.

Diagnosis—The case was diagnosed as acute termination of a chronic lymphatic leukemia.

Course—In the succeeding five days, the patient became moribund, the temperature rose to 101 F, râles developed in the bases of the lungs and he died on Feb. 26, 1930.

Postmortem Examination—The body was that of a white man. The skin was grayish white. The left cheek and both eyelids were markedly swollen, and there was marked ecchymosis of the left eye. From the left ear there was a discharge with a foul odor. The lips were pale, most of the teeth were absent, and the gums were swollen, dirty gray and in places covered by foul-smelling, soft, brownish membranes.

The right posterior cervical glands were shotlike. The anterior cervical glands formed huge masses under the lower jaw. Enlarged glands were present in the left axilla and in the groins. The abdomen was slightly distended.

The thoracic cavity revealed circumscribed adhesions about the lateral and posterior aspects of the right lung. The lungs were distended, the upper lobes crepitant and the lower lobes subcrepitant. The pleurae were purplish gray. The cut surface was purplish gray and moderately moist. The lymph glands at the hilus measured as much as 10 mm, at the bifurcation, as much as 20 mm. They were firm and mottled gray.

The heart weighed 345 Gm. The myocardium was brownish gray and friable. The left ventricle was slightly dilated. The aorta was smooth. The coronary vessels were thin-walled.

The thyroid gland weighed 35 Gm and was uniform and light brown.

The stomach was enormously enlarged. The mucosa was much thickened and thrown up into huge convolutions giving it a brainlike appearance. These convolutions were as much as 2 cm thick and 2 cm high. They were firm and covered by smooth, pale mucosa and a small amount of blood-tinted mucus. The folds marking the pathway of the stomach were well preserved (fig. 1).

In the duodenum, especially adjacent to the pylorus, there were polyp-like, firm, grayish-white masses as much as 10 mm in diameter and 10 mm high.

Throughout the entire small intestine there were numerous plaque-like nodular masses. These measured, on an average, 55 by 30 mm in diameter and 10 mm in height. They were moderately firm and subdivided by deep depressions. They varied in color from light yellowish gray to light pink. In the lowermost portion of the ileum, these changes were most marked. Here there were huge, polyp-like plaques measuring 6 by 4 by 16 cm. Their free surfaces were ulcerated, others were hemorrhagic (fig. 2).

The appendix was 8 cm long and 15 mm thick. It was firm.

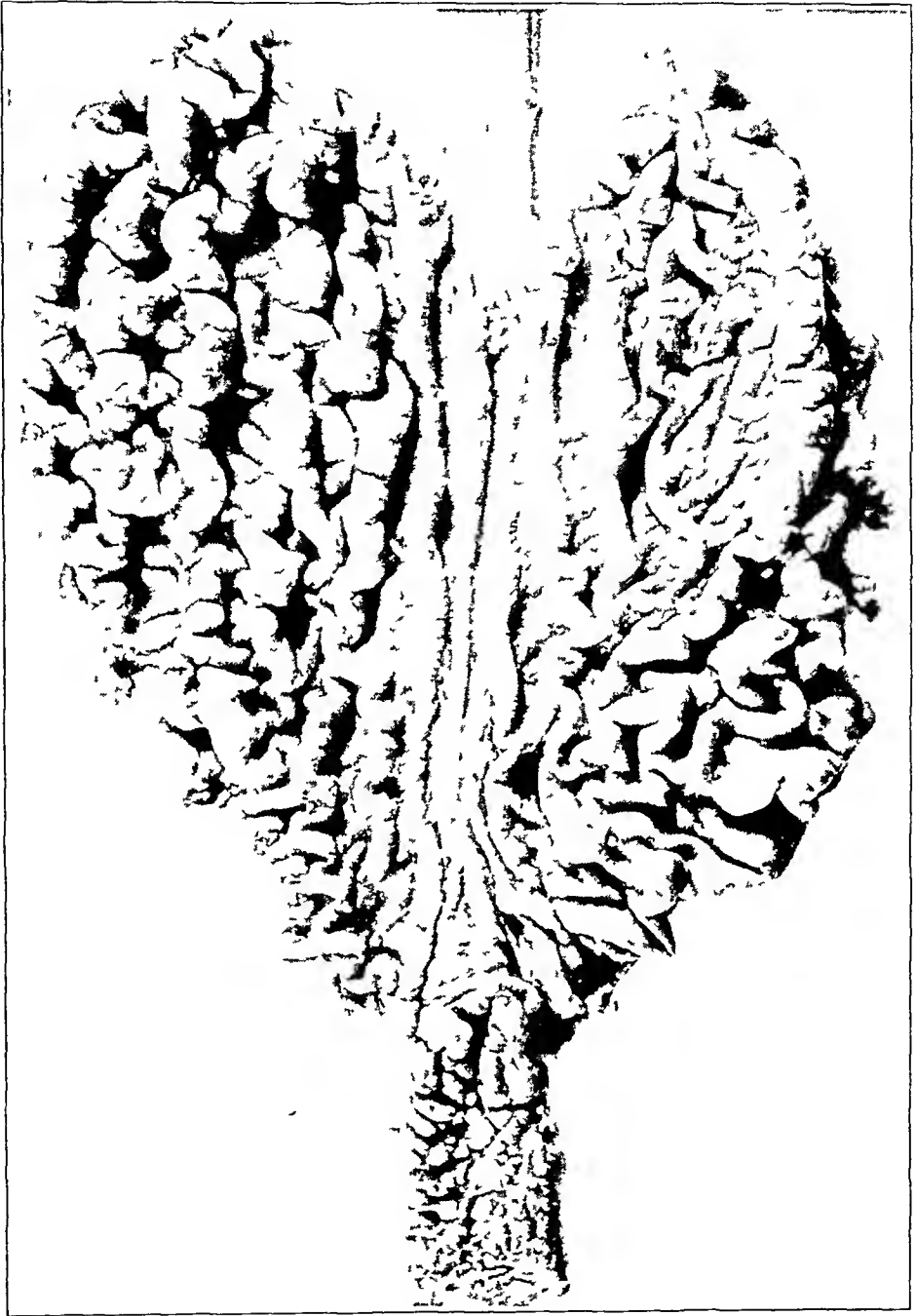


Fig 1—Stomach opened along greater curvature, showing diffuse infiltration with enormous enlargement and “bramlike” rugae

The mucosa of the large intestine was light gray. Throughout the entire length of the intestine were numerous firm, grayish-white nodules averaging 3 mm in diameter.

The mesenteric lymph glands of the radix were matted together into a solid, lobulated mass, 13 by 9 by 6 cm. On cut surface, the outline of the single glands was indistinct. The color was grayish white mottled with purplish red. A milky fluid could be removed. The large mass was surrounded by numerous smaller glands from 10 to 55 mm in diameter. The glands were medullary and varied in color from light pinkish gray to yellowish gray (fig 2).

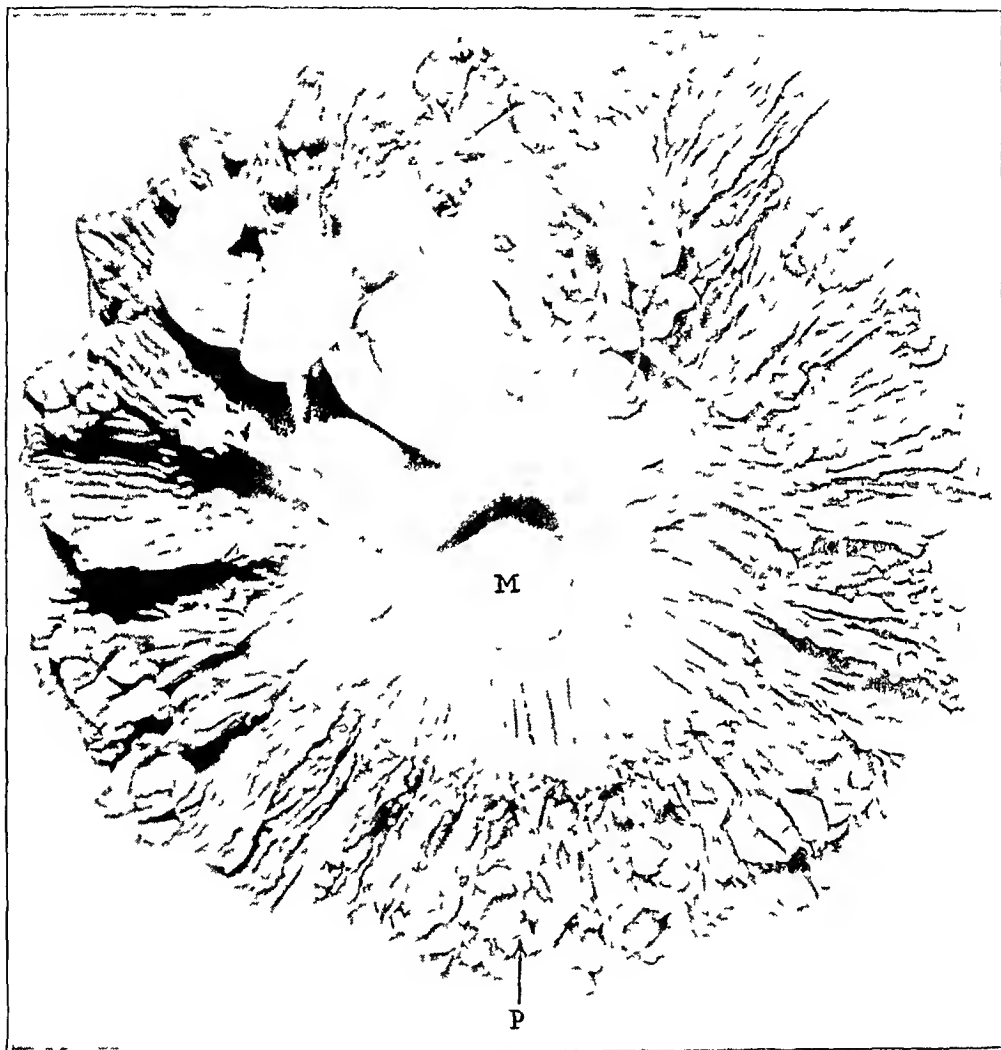


Fig 2—Ileum with mesentery showing polypoid infiltrations (P) and huge mesenteric lymph glands (M)

The suprarenal glands weighed 11 Gm. The cortex was 1 mm wide and pale gray-brown with light yellow areas.

The spleen weighed 2,865 Gm and measured 30 by 22 by 8 cm. At the hilus, a spherical aberrant spleen measured 4 cm in diameter. It was moderately firm. The surface was mottled deep purplish gray and purple-pink, and on the upper one third of the convex surface there were whitish areas as large as 5 by 4 mm, arranged in groups about a purple-gray, firmer area. The cut surface was purplish red. The pulp everted slightly. There were numerous indistinct grayish-white areas from pinpoint size to 1 mm in diameter. The firm area extending

for 25 cm into the parenchyma, was sharply separated and light pink-gray. The aberrant spleen was light purplish pink with numerous light gray nodules. The lymph glands at the hilus measured 30 by 15 by 6 mm, and were firm and light gray or purplish gray.

The liver weighed 3,610 Gm and measured 37 by 26 by 11 cm. The surface was smooth and purplish brown with small purplish-red patches and light-brown and grayish-white lines and patches. The cut surface was light purplish brown with numerous whitish areas and lines as much as 2 mm in diameter. The periportal septums were prominent.

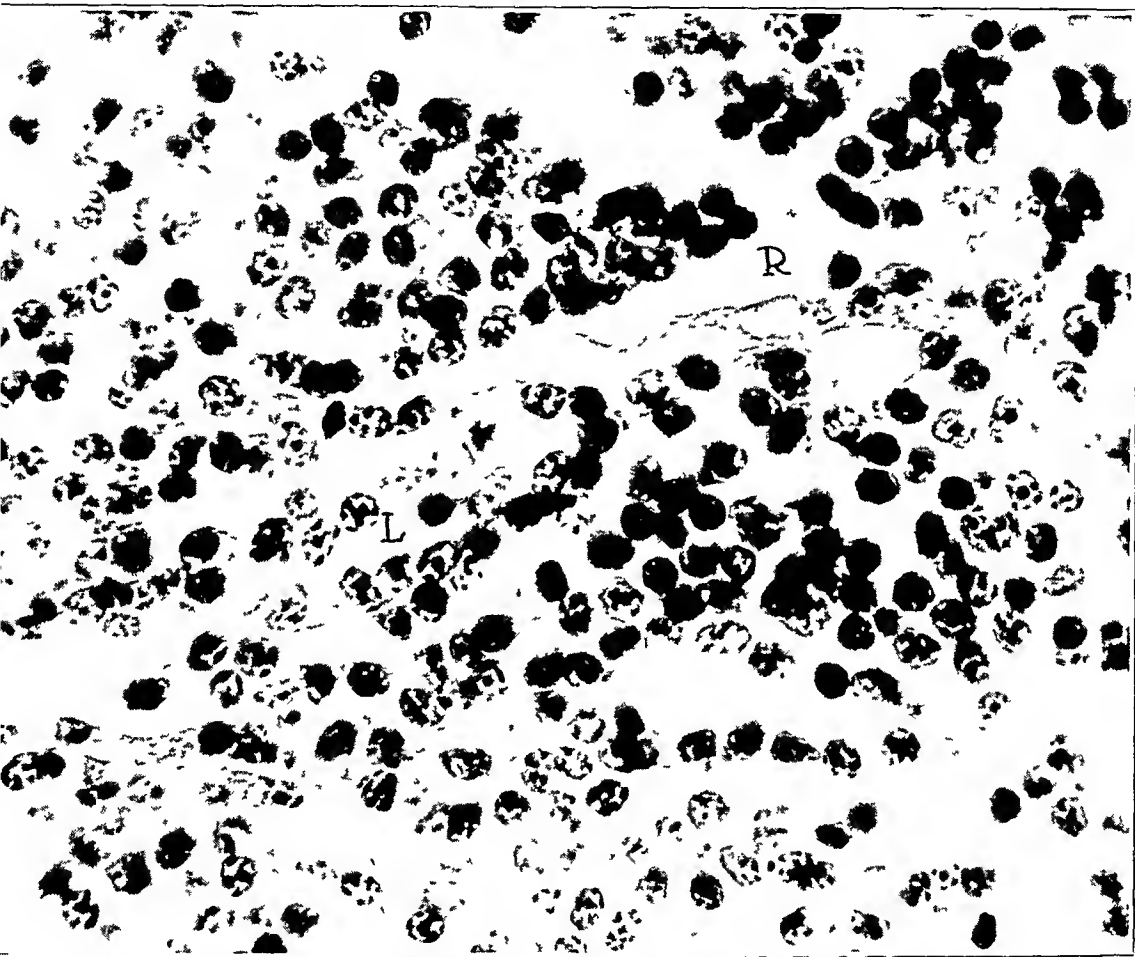


Fig. 3—Section through polypoid mass in ileum, showing the lymphocytes (L) and reticulum cells (R) composing the infiltration, hematoxylin and eosin stain, oil immersion lens, $\times 1,200$

The gallbladder was filled by thin, light yellow-brown bile. The lymph glands at the hilus measured as much as 20 mm in diameter and were firm and light gray-brown.

The pancreas weighed 75 Gm. It was firm, light gray-brown and lobulated. The peripancreatic lymph glands measured as much as 40 by 20 by 15 mm, and were moderately firm and light gray-white with pinpoint-sized whitish areas.

Microscopic Examination—In a Peyer's patch in the intestine, the huge plaques still retained their composition of single nodes which were separated by strands

of connective tissue. These strands were often loosely infiltrated by cells of the same type as those of which the nodes were composed. The nodes still showed a differentiation into lighter and darker stained areas. The darker stained areas were composed of round cells slightly larger than lymphocytes, each with a round nucleus rich in fine chromatin granules. There were no distinct nucleoli. The nucleus was surrounded by a narrow rim of cytoplasm (fig 3). Between these cells were found single elements, each with an ample, lightly stained cytoplasm and a vesicular nucleus. These follicle-like areas were separated by anastomosing strands, which, in addition to the round cells, contained a large number of the

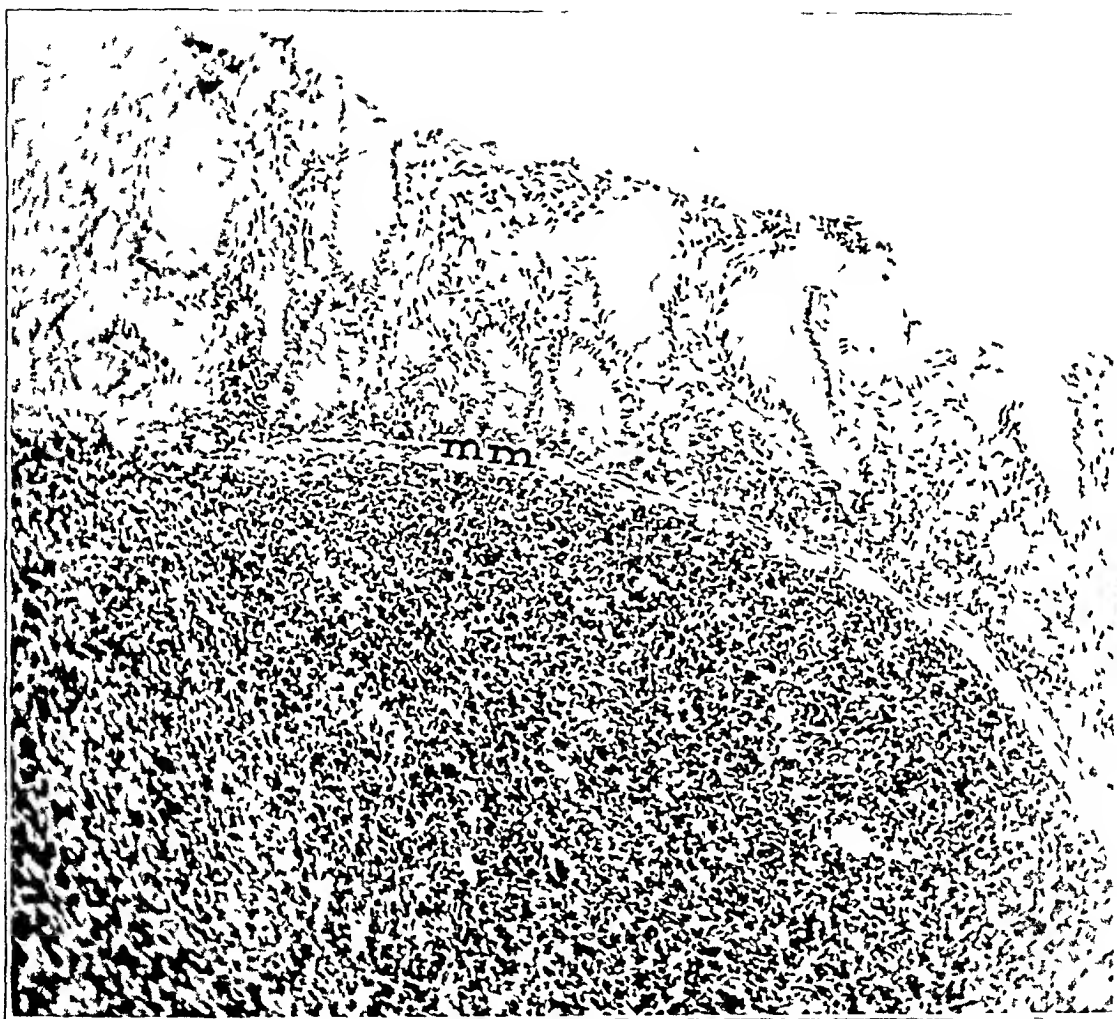


Fig 4—Lower magnification of the tissue pictured in figure 3, showing restriction of the infiltration to the submucosa, the muscularis mucosa (*mm*) being intact, hematoxylin and eosin stain, $\times 80$

pale-stained cells, a number of which were filled by dark brown pigment granules. In these strands, the capillary vessels and reticulum were more prominent than in the dark areas. The entire structure was well circumscribed and located in the submucosa (fig 4). The strands of the dark-nucleated round cells extended between the muscle fibers of the muscularis propria to become slightly more abundant in the zone between the two layers. The subserosa appeared loosened and contained a few small accumulations of the same type of cells. The extension into the periphery was much more marked on the internal surface of the node, where in many places the muscle fibers of the muscularis mucosa were widely

separated, and the basal portions of the glands were embedded in dense accumulations of the round cells. The lining epithelium of the glands was well preserved, and there was an increased number of goblet cells. The capillaries were dilated and contained a varied number of the cells of which the nodes were composed.

In the plaque in the upper jejunum, the picture almost exactly paralleled that described in the preceding paragraph, except that the nodules were smaller. The lighter areas were absent, the strands between the nodes much broader and the muscularis mucosa and muscularis propria intact.

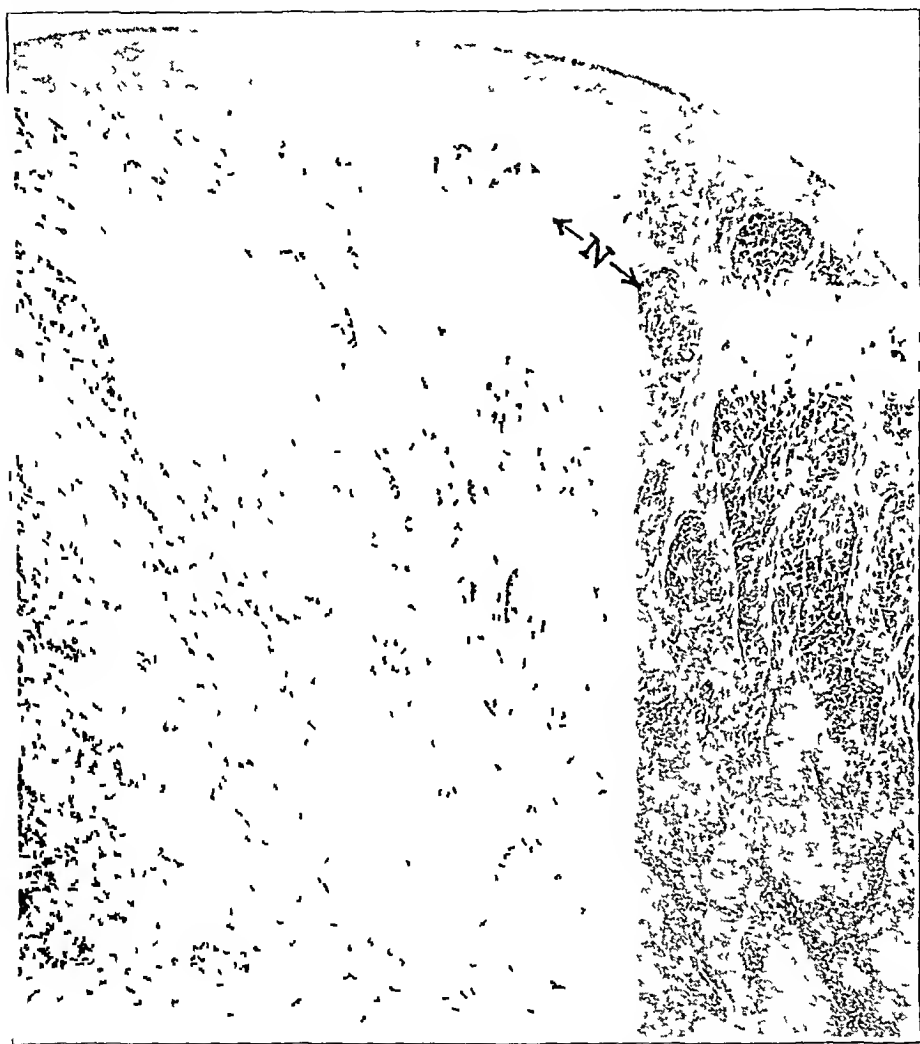


Fig 5—Section through the top of a single ruga of the stomach, showing the infiltration of the mucosa and submucosa, the composition of distinct nodes (N) is still apparent, hematoxylin and eosin stain, $\times 15$

A section through a single ruga of the stomach revealed that the submucosa and the mucosa formed a convolution which was enormously thickened by the presence of huge nodes similar to those described in the Peve's patch (fig 5). Running through the center of the fold was a thin strand of dense connective tissue loosely infiltrated by the cells of which the nodes were composed. Between the nodes, the strands of connective tissue were similarly infiltrated. The division of the nodes into a darker, narrower periphery and a broad, lighter center was

much more distinct than in the Peyer's patch. The component cells were the same except that the larger cells with ample cytoplasm and vesicular nuclei were much more abundant. The muscularis mucosa was practically absent, and the glands were narrow, thin and far apart. In an occasional area the glands penetrated deep into the submucosa, forming a narrow wedge. However, even here there was much interglandular infiltration. The parietal cells were abundant in such areas. In the shallower glands, which probably represented only the foveolae, the cells alone were present.

The infiltration extended between the layers of the muscularis propria and into the subserosa. The blood vessels were filled with the small darkly nucleated cells.

The tumor of the mesenteric lymph gland was composed of dark-nucleated round cells of the size of lymphocytes, or slightly larger. Between these cells were found a few large, irregularly shaped cells with vesicular nuclei. There were areas in which cells of the latter type were more numerous and showed in the cytoplasm a great many dark, round, coarse chromatin granules. The separation into follicle-like areas was still visible, but less marked than in the Peyer's plaque of the intestine. Mitotic figures could not be found. There was a great uniformity in the shape and structure of the nuclei. The adventitia of the superior mesenteric artery was densely infiltrated by the round cells. The infiltration stopped abruptly at the muscularis.

In the axillary lymph glands, the difference between cortex and medulla was obscured, but the separation between follicles and interfollicular tissue could still be recognized. The cells were of the type of the small lymphocyte or slightly larger and scattered between them was a varied number of pigment-filled cells. The capsule, though still visible, was infiltrated by lymphoid cells, and the infiltrations also seemed to continue into the periglandular tissue, but the latter changes were rather insignificant, so that the gland still appeared as a well defined unit.

The inguinal lymph node resembled the axillary lymph nodes, the capsular infiltration was marked. There were areas that were uniformly composed of dark-nucleated round cells and did not show the differentiation into follicles and interfollicular tissue.

The submaxillary gland contained large accumulations of dark-nucleated round cells, which were arranged about the larger ducts and blood vessels and which separated the lobules, following the ducts, they extended into the lobules. Even the small ducts were occasionally found surrounded by a heavy coat of round cells. These cells, however, did not extend into the epithelial lining of the ducts which were perfectly preserved. Thin strands of cells were found closely adjacent to the basement membrane of the glandular tubuli, but did not penetrate it. The glandular structure otherwise was unchanged, and mucinous and albuminous glands were found in the different morphologic stages of secretory activity. The gland was surrounded by much loose fibrillar connective tissue which contained numerous small and larger accumulations of lymphoid round cells. This tissue gradually passed into the capsule of the lymph glands, the structure of which was somewhat obscured by an enormous hyperplasia of the lymphatic elements.

In the spleen, the follicles were not sharply separated from the pulp. The cords were composed chiefly of cells of the same type as those that formed the follicles. A certain differentiation into follicles and pulp resulted from the marked blood content of the latter. The sinuses were wide, the endothelium was flat, and the lumen was filled by erythrocytes and many lymphoid cells. The capsule was thin. The trabeculae, too, were thin and scanty and were not invaded by the round cells. In the sheaths of the larger blood vessels were many cells that were filled by dark brown pigment.

In the liver, the periportal tissue was so densely infiltrated by dark-nucleated round cells that the portal septums looked like lymph follicles. The bile ducts were embedded in these cells, but were well preserved, as were the branches of the hepatic artery, while the branches of the portal vein were compressed and obscured. From the acini, the cellular infiltrations were sharply separated, and only in a few places was there an extension into the portal capillaries. The portal capillaries throughout the acini were dilated and, in addition to erythrocytes, contained a great many dark-nucleated round cells. The Kupffer cells were swollen, and many of them contained brown pigment granules. Pigmented cells also were present in the portal septums. The outer coats of the sublobular veins also were infiltrated by the round cells, and in places these infiltrations involved the entire wall, projecting into the lumen in the form of small nodules.

The kidney showed numerous dense perivascular accumulations of dark-nucleated round cells throughout the cortex and at the corticomedullary border. These infiltrations extended between the adjacent tubuli and surrounded the adjacent glomeruli, which, however, were not invaded. The capsule was much thickened and was uniformly infiltrated by the small round cells. There was a slight swelling of the epithelium of the convoluted tubuli, with a moderate capillary hyperemia.

The bone-marrow was very cellular. The predominating type of cells was round with a scanty cytoplasm and a round nucleus rich in chromatin. The latter formed granules of varying size. The majority of these cells were larger than lymphocytes. Between these cells were found single elements with a more abundant cytoplasm and lighter-stained nuclei and cells with a coarse, oxyphil granulation. There were a few small groups of polymorphonuclear leukocytes and single megakaryocytes with pale-stained and indistinct nuclei. Nucleated red cells were scanty. The fat cells between these cellular accumulations contained a network of delicate fibrils. The reticulum cells were swollen.

The small bronchi were dilated and filled by dense clumps of cells, polymorphonuclear leukocytes by far predominating. There were only a few dark-nucleated round cells. In the walls of the bronchi, there were nodular, circumscribed accumulations of dark-nucleated lymphoid round cells. The alveolar capillaries were dilated and filled by blood and lymphoid round cells. In the alveolar spaces were mononuclear cells with coal dust, a varying number of polymorphonuclear leukocytes and a few lymphocytes. Groups of alveoli were filled by erythrocytes.

Anatomic Diagnosis—The diagnosis was chronic lymphatic leukemia with acute termination, extensive lymphatic infiltrations of the stomach and intestines, huge leukemic tumor of the spleen with anemic infarct, leukemic infiltration of the liver, kidneys and submaxillary glands, enormous hyperplasia of the mesenteric lymph glands, hyperplasia of the axillary, inguinal, left submaxillary, periaortic, peribiliary, peripancreatic and perigastric lymph glands, parenchymatous degeneration of the myocardium and dilatation of the left cardiac chamber, anemia and edema of the brain, chronic otitis media of the left side, gangrenous stomatitis, partial fibrous obliteration of the right pleural cavity, passive hyperemia and edema of the lungs and purulent bronchitis, slight sclerosis of the coronary arteries, and lymphoid bone-marrow.

COMMENT

In brief, the case described was that of chronic lymphatic leukemia terminating acutely. The pathologic observations were remarkable

because of the extensive involvement of the gastro-intestinal tract. The stomach was enormously enlarged with huge convolutions on the inner surface, giving it a brainlike appearance. The small and large intestines were beset with huge plaques and polyp-like masses. The microscopic examination of the stomach revealed an infiltration of the mucosa and submucosa by confluent lymphoid nodules. The intestinal changes were restricted to submucosal infiltrations composed of similar nodules. Slight regressive processes in the form of superficial ulcerations and hemorrhages were present. The spleen was unusually large—for lymphatic leukemia.

In leukemia there exists no proportion between the symptoms arising from the gastro-intestinal tract and the pathologic changes therein. Most extensive changes may be symptomless. General factors such as anemia and cachexia, may produce far more gastro-intestinal complaints than the most advanced leukemic involvement.

Distribution of Lesions in the Gastro-Intestinal Tract in Fourteen Cases of Various Leukemias

Type of Leukemia	Petechiae	Profuse Hemorrhage	Diphtheritic Colitis	No Change	Leukemic Infiltration
10 acute myelogenous	4	1	1	2	2 cases (1) appendix (2) Peyer's patches
1 chronic myelogenous			1		
2 chronic lymphatic leukemia	1				Brainlike stomach with polyps in intestine
1 acute lymphatic	1				

The anatomic changes in the stomach and intestines may be divided into nonspecific and specific. The nonspecific changes are part of the hemorrhagic diathesis which accompanies the acute disease and which develops terminally in the chronic. The specific changes result from leukemic infiltration.

The nonspecific changes consist primarily of hemorrhages. These may take place into an unchanged segment or one leukemically affected (Singer²).

In fourteen cases of various leukemias, nine showed the effects of hemorrhages, but were free from infiltration (table).

The hemorrhages may be slight or severe. In a case of acute myelogenous leukemia in a child of 6 years, the onset was sudden with chill, fever, bloody diarrhea, profuse hematemesis and purpura. Post mortem, the gastro-intestinal tract was filled by blood. There were, however, no specific leukemic changes.

² Singer, G., in Kraus, F., and Brugsch, T. *Spezielle Pathologie und Therapie innerer Krankheiten*. Vienna, Urban & Schwarzenberg, 1922, vol. 6, pp. 1 and 774.

Severe hemorrhages rarely result from the opening of a blood vessel by the secondary ulceration of a leukemia infiltrate. Eichhorst³ described a fatal hemorrhage due to such a process opening into a gastric vein.

Secondary changes soon follow the hemorrhages. The devitalized tissues are invaded by bacteria. Ulcerations and sloughs result which may be circumscribed or extensive, basing the submucosa over large areas. The latter cases closely resemble dysentery or uemia (Jaffe⁴). Two of my patients with leukemia showed a diffuse pseudomembranous colitis and proctitis. One (with acute myelogenous leukemia), however, had received asphenamine three weeks prior, and the other (with chronic myelogenous leukemia) had received extensive roentgen therapy, factors both of which may have contributed to the condition of the colon.

Hemorrhagic and ulcerative changes may complicate specifically affected parts. These secondary changes may be due to a variety of causes, such as circulatory disturbances in polypoid infiltrations or resulting from capillary compression by dense infiltration, inadequate reaction of the infiltrated tissues to trauma, bacteria or hemorrhagic diathesis. Such ulcerative processes may be restricted to the Peyer's patches and be indistinguishable from typhoid ulcerations. Even the clinical picture in such cases may exactly simulate typhoid (Denning,⁵ Heixheimer⁶). In the past, much confusion arose, and some authors thought of combinations of the two diseases (Voswinkel and Dunzelt⁷). The deep extension of ulcerations has occasionally resulted in local and diffuse peritonitis (Hansemann,⁸ Pal⁹).

The specific changes in the gastro-intestinal tract have been extensively reviewed by Hoffmann,¹⁰ Heixheimer,⁶ Schultze¹¹ and Singer.² Much variation exists with reference to the extent, location and type of involvement. The entire gastro-intestinal tract from cardia

3 Eichhorst, H. Ueber acute Leukämie, *Virchows Arch f path Anat* **130** 365, 1892

4 Jaffe, R. H. Personal communication to the author

5 Denning, A. Ueber acute Leukämie, *München med Wchnschr* **47** 1297, 1900

6 Heixheimer, G. Ueber die Lymphoblasten (grosszellig) lymphatische und Myeloblasten Leukämie, *München med Wchnschr* **60** 2506 and 2573, 1913

7 Voswinkel and Dunzelt, cited by Singer (footnote 2, p 779)

8 Hansemann. Demonstration von Präparaten, *Verhandl d Berl med Gesellsch* **23** 89, 1892

9 Pal, cited by Hoffmann (footnote 10)

10 Hoffmann, M. Ueber Veränderungen des Magen-Darmkanales bei Leukämie. *Inaug Diss*, Friedrichs Universität, 1905

11 Schultze, W. Ein Beitrag zur Kenntnis der akuten Leukämie, *Beitr z path u z allg Path* **39** 252, 1906

to rectum may be infiltrated or only a single subdivision, as the appendix. Infiltration of the latter alone occurred in one of my cases of acute myelogenous leukemia (see following paragraphs and the table), and a similar observation was reported by Lehdorf¹². The infiltrations may restrict themselves to the Peyer's patches, to the lymphoid follicles or to the nonlymphoid tissue between them. In addition to focal or nodular, diffuse infiltrations may occur, so that the organ becomes reproduced on a much exaggerated scale. Any portion of the gastro-intestinal tract may be thus affected (stomach, stomach and intestines [Biggs and Elliot¹³], colon [Barnick¹⁴]).

The depth of infiltration varies from one to all layers of the intestinal wall (Mullern and Grossmann¹⁵).

The various types of leukemia affect the gastro-intestinal tract differently. In myelogenous leukemia, the changes are usually not extensive. Naegeli¹⁶ denied having ever seen any myeloid changes in the intestine. Mullern and Grossmann,¹⁵ Schultze¹¹ and Heixheimer⁶ described infiltrations of the ileum and colon which were located between the lymphoid structures of the intestine. Hoffmann,¹⁰ in addition, described submucosal and mucosal myeloid infiltration of the stomach without involvement of the lymphoid follicles. Kahn¹⁷ studied a case of acute myelogenous leukemia in which a myeloid nodule was found in the stomach and smaller nodules in the ileocecal region and rectum. Despite the extensive myeloid transformation of the lymphoid structures throughout the body, those of the intestine were not invaded and were even hyperplastic.

In eight of my ten cases of myelogenous leukemia (nine acute and one chronic ending acutely), specific changes were absent. In the ninth case, the appendix was 9 cm long, with a wall 5 mm thick. Microscopic examination revealed a diffuse infiltration of the entire wall by large round cells each with a round or oval nucleus and a granular chromatin net with one or two small nucleoli. Their cytoplasm was narrow and basophil and contained a fine, dustlike oxydase granulation. Other cells contained a coarse oxyphil granulation. In the tenth case,

12 Lehdorf, H. Ueber Lymphocytenleukämie im Kindesalter, Wien med Wchnschr 56 311, 1906

13 Biggs, A. O., and Elliot, A. R. Pseudoleukemia Gastro-Intestinalis, J. A. M. A. 83 178 (July 19) 1924

14 Barnick, O. Veränderungen im Kehlkopf und in der Trachea bei Leukämie, München med Wchnschr 45 589, 1898

15 Mullern, K. V., and Grossmann, B. Beiträge zur Kenntnis der primären Erkrankungen der hämatopoetischen Organe, Beitr. z. path. Anat. u. z. allg. Path. 52 276, 1912

16 Naegeli, O. Die Leukämien, Blutkrankheiten und Blutdiagnostik, Berlin, Julius Springer, 1923, pp. 370-441

17 Kahn, F., cited by Singer (footnote 2)

the Peyer's patches were prominent, measuring 4 by 2 cm in diameter and 5 mm in height, and were superficially ulcerated. They were composed of large round cells with an ample cytoplasm that contained a fine granulation. The nuclei were round, oval or slightly indented, with fine chromatin granules. There were also small groups of huge myeloblasts. Scattered between these cells but more numerous at the periphery of the plaques were small lymphocytes. Polymorphonuclear leukocytes and eosinophil granulocytes were scanty. The plaques were surrounded by recent extravasations of blood, and the superficial layers were completely necrotic. Outside the plaques, the submucosa contained focal accumulations of the large round granulated cells, loosely scattered plasma cells, leukocytes and lymphocytes and many histiocytes. Small perivascular groups of granulated cells were seen in the subserosa.

From my own cases and others it may therefore be said that specific gastro-intestinal changes in myelogenous leukemia are not extensive. The same may hold true of the aleukemic myeloses.

In the lymphatic leukemias, however, the condition is different.

Most extensive gastro-intestinal changes have been described in pseudoleukemia. Wells and Maver¹⁸ in 1904 reviewed 238 such cases, in 8 of which they found the stomach and intestines so transformed as to entitle the conditions to characterization as a distinct pathologic syndrome with the distinctive name of pseudoleukemia gastro-intestinalis. In 5 of these cases, the stomach was diffusely infiltrated, vastly enlarged and showed an inner lining thrown up in "immense loose sinuous folds like cerebral convolutions." The small and large intestines showed both diffuse and circumscribed nodular or polypoid infiltrations.

Symmers¹⁹ in 1909 brought the number of such cases to eleven and recently Biggs and Elliot¹⁸ collected thirteen cases, to which they added one of their own showing diffuse infiltration of the entire tract from cardia to rectum. The latter authors also contributed the only roentgen study ever reported, in which such a "brainlike" stomach was revealed as a small, immobile stomach of irregular outline but with a perfect bulb.

Analysis of the fourteen cases reveals that much confusion exists. Not all of the cases are of the same character. Some are leukemias and some are Hodgkin's lymphogranuloma, but all are called pseudoleukemia. Originally, Cohnheim²⁰ characterized as pseudoleukemia pathologic syndromes identical with leukemia but without the blood picture, what is now called aleukemic leukemia. But subsequent authors

18 Wells, H. G. and Maver, M. B. Pseudo-leukemia Gastro-intestinalis, *Am J M Sc* **182** 837, 1904.

19 Symmers, D. Certain Unusual Lesions of the Lymphatic Apparatus, *Arch Int Med* **4** 218 (Sept.) 1909.

20 Cohnheim. Ein Fall von Pseudoleukämia, *Virchows Arch f path Anat* **33** 451, 1865.

have applied the term to widely different diseases, as Hodgkin's lymphogranuloma, aleukemic leukemia, Banti's disease, tuberculosis, etc. Much confusion has thus arisen. Thus Wells and Maver¹⁸ named their own case and the seven that they gathered from the literature pseudoleukemia gastro-intestinalis, and meant thereby Hodgkin's lymphogranuloma. In their series there were undoubtedly such cases, including their own. But the remainder were indisputably examples of aleukemic lymphadenosis (cases of Carrington,²¹ Schlesinger²¹ and Stoerck²¹).

Symmers, on the other hand, although he retained the name pseudoleukemia gastro-intestinalis, considered his and Wells and Maver's¹⁸ cases as aleukemic leukemia in the original sense of Cohnheim²⁰. Subsequent authors followed Symmers (Ewing,²² Biggs and Elliot¹³).

It would avail little to go extensively into the question. That both are right there can be no doubt. Diffuse and polypoid infiltrations in the stomach and intestines can occur in both lymphogranuloma and aleukemic lymphadenosis. Symmer's¹⁹ case is indisputably the latter and Wells and Maver's¹⁸ the former. A typical brainlike stomach in Hodgkin's disease was contributed by Scott and Forman²³ among others.

When in 1918 Symmers²⁴ again reviewed the subject, he stated that in nineteen cases of chronic lymphatic leukemia he had found no gastro-intestinal infiltrations. From the extensive infiltrations that he had found in pseudoleukemia (aleukemic lymphadenosis) he concluded that lymphatic leukemia and pseudoleukemia are vastly dissimilar diseases and advised classifying the latter with the sarcomas. My case is therefore of much significance, since there can be no question of its nonsarcomatous nature. Gastro-intestinal infiltrations in chloroma (Lehndorff²⁵) and lymphosarcoma (Kundrat²⁶) are known. But in my case there were to be noted absence of cellular anaplasia, absence of mitotic figures and restriction of the growth to the capsules of the gland and to natural boundaries. There was no interglandular infiltration. From all points of view, the case is one of chronic lymphatic leukemia of the ordinary type. Therefore, the complete correspondence of the cases of pseudoleukemia gastro-intestinalis with my case of leukemia

21 Cited by Symmers (footnote 19)

22 Ewing, J. *Neoplastic Diseases*, ed 3, Philadelphia, W. B. Saunders Company, 1928, pp 410-411

23 Scott, E., and Forman, J. *Lymphoblastoma of the Gastro-Intestinal Tract with Report of a Case of Hodgkin's Disease of the Stomach*, Ohio State M. J. **12** 323, 1916

24 Symmers, D. *Relationship of the Toxic Lymphoid Hyperplasias to Lymphosarcoma and Allied Diseases*, Arch. Int. Med. **21** 237 (Feb.) 1918

25 Lehndorff, H. *Chlorom*, Ergebn. d. inn. Med. u. Kinderh. **6** 221, 1910

26 Kundrat, cited by Singer (footnote 2, p 791)

gastro-intestinalis in both the gross and the microscopic features establishes beyond doubt the identity of the two diseases Jaffé²⁷ in 1927 pointed out the relationship of the aleukemic to the leukocythemic leukemias and expressed himself as dissatisfied with prevalent theories concerning the quantitatively and qualitatively negative blood pictures in aleukemic leukemia Lack of chemotactic stimulant, loss of the vascular connections of atypical blood-forming tissues, destruction of the abnormal cells in the blood stream are all insufficient, as King²⁸ had already described spontaneous aleukocythemic phases in chronic myelogenous leukemia (Jaffé²⁷)

That none of the existing prevalent opinions concerning the cause of aleukocythemia in leukemia are satisfactory is most strikingly shown by my last case which commenced as an aleukemic lymphadenosis and terminated as an acute lymphoblastic leukemia

J S, aged 19, a Filipino, entered the Cook County Hospital on Nov 26, 1929 His complaint was rapidly increasing bilateral swelling of the neck This had commenced one month before following a tonsillectomy It made breathing difficult Physical examination revealed, essentially, generalized lymphadenopathy

A most careful examination of numerous blood slides gave negative results A biopsy yielded the diagnosis aleukemic lymphadenosis, in view of the negative results of examination of the blood

The patient received x-ray treatment, improved and returned home on Dec 21, 1929 Two months afterward (on Feb 17, 1930), he returned with the complaint of marked weakness and bleeding from the nose

Reexamination substantiated the previous observations, except that the blood now showed a red blood cell count of 1,500,000, a hemoglobin content of 40 per cent and a white blood count of 53,000, which on differential study was composed of 79 per cent lymphoblasts, 16 per cent lymphocytes and 5 per cent neutrophils The diagnosis of acute lymphoblastic leukemia was made, which was substantiated by autopsy

We have, then, here in one case aleukemic and leukocythemic phases of the one disease—lymphatic leukemia In the words of Marchand,²⁹ “the essential changes in leukemia are the anatomical and not the hematologic”

Although nodular and polypoid infiltrations are described as occurring in the intestine and stomach in lymphatic leukemia (Marchand²⁹), I have not been able to find in the literature a case similar to my own other than those described as pseudoleukemia gastro-intestinalis This makes the condition rare

Clinical symptoms in gastro-intestinal leukemia may be absent or they may consist of diarrhea, enterorrhagia and abdominal pain In

27 Jaffe, R H Aleukemic Myelosis, Arch Path 3 56 (Jan) 1927

28 King, cited by Jaffe (footnote 27)

29 Marchand Zwei Falle von Leukämie lymphatica, Munchen med Wchnschr 55 422, 1908

two cases with polypoid infiltration in the ileum, intussusception occurred (Hoffmann,³⁰ Celler²¹) Perforation peritonitis has been mentioned in a foregoing paragraph

SUMMARY

1 Fourteen cases of leukemia, eleven myelogenous and three lymphatic, were studied with reference to the gastro-intestinal involvement

2 Nonspecific changes were found in nine cases of acute myelogenous leukemia, consisting of hemorrhages, ulceration and secondary inflammatory processes In two cases (acute myelogenous leukemia) there were no changes

3 Specific changes were found in two cases of acute myelosis, consisting of an infiltration of the appendix and an infiltration of Peyer's patches, respectively

4 Specific changes were found in one case of chronic lymphatic leukemia The stomach was enormously enlarged, with huge convolutions on the inner surface, giving it a brainlike appearance, and the intestines were beset with plaques and polyp-like infiltrations

5 In reviewing the literature, another such case was not discovered The case was found, however, to parallel exactly those described as aleukemic lymphadenosis or pseudoleukemic gastro-intestinalis

6 From these facts it is concluded that the aleukemic and leukocythemmic leukemias are fundamentally identical

7 In further support of this conclusion a last case is described in which an aleukemic lymphadenosis terminated as an acute leukocythemmic lymphadenosis

8 The symptoms in leukemia gastro-intestinalis are briefly discussed, and their importance is emphasized

30 Hoffmann, M Ueber klinische Erscheinungen bei Gastro-intestinale Pseudoleukämie, Arch f klin Chir 82 794, 1907

A CRITIQUE OF PRESENT METHODS FOR THE STUDY OF GASTRIC ACIDITY *

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The problem of gastric acidity has interested us for some time. An analysis of the different methods for studying gastric acidity reveals certain disadvantages and inaccuracies. Our attention has been particularly focused on the problem because of the conflicting observations in patients with partial gastrectomies. In these patients, the factor of regurgitation of alkaline intestinal secretions is an important consideration.

DIRECT METHODS

We feel that the stimulation of gastric secretion by the ordinary test meals in use (gruels, crackers, water, etc.) is uncertain and variable. Psychic elements, such as appetite or distaste for food, speed of eating and quantity of saliva are factors that make accurate results difficult. Babkin¹ recently emphasized the influence of the secretion of mucus on gastric acidity. Furthermore, the ingestion of a meal does not always afford a maximum stimulus, as is noted in those patients who appear to have anacidity, but who subsequently secrete hydrochloric acid freely after a more powerful stimulus, such as that given by histamine. The buffer substances in the various test meals may combine with significant amounts of free hydrochloric acid. The regurgitation of alkaline intestinal secretion may be sufficient to neutralize small amounts of free acid in patients with hypo-acidity, and a fallacious diagnosis of achylia gastrica may thus be made. The frequent use of several glasses of fluid with the routine test meal introduces the factor of dilution.

The use of neutral red has been investigated by Finkelstein,² Piersol, Bockus and Banks,³ Winkelstein and Marcus⁴ and others. It has been affirmed that the failure of neutral red to be excreted into the stomach within two hours after intramuscular injection invariably means true

* Submitted for publication, June 23, 1930

¹ From the Gastro-Intestinal Department, Jewish Hospital

1 Babkin, B. P. Am J Surg **7** 498 (Oct.) 1929

2 Finkelstein, R. Arch f Verdauungskr **30** 299, 1923

3 Piersol, G., Bockus, H., and Banks, J. Tr. A. Am. Physicians **40** 413, 1925

4 Winkelstein, A., and Marcus, J. Excretion of Neutral Red in Stomach in Achylia Gastrica, J. A. M. A. **92** 1238 (April 13) 1929

achlorhydria The presence of neutral red in the gastric contents means that the stomach is capable of secreting free hydrochloric acid

Piersol, Bockus and Banks⁵ have shown experimentally that neutral red is eliminated in the gastro-intestinal tract not only by the stomach, but also by the whole of the small bowel to the ileocecal junction, as well as in the bile and in the urine The finding of neutral red in the extracted gastric specimen must therefore be guardedly interpreted, especially since in our experience significant amounts of bile have been found in the gastric extractions of patients with partial gastrectomies The possibility of neutral red being regurgitated with duodenal contents into the stomach must always be considered

Medes and Wright,⁶ in their studies of duodenal regurgitation, showed that regurgitation of duodenal contents into the fasting stomach occurs with great frequency The regurgitated materials may include bile, pancreatic juice (trypsin) and secretion of the duodenal mucosa (sucrase) They have shown that these may occur together or any one independently Bile is regurgitated rarely without trypsin, trypsin much more frequently without bile Since the possibility of duodenal regurgitation is frequent because of the patency of the pylorus in cases of subacidity and anacidity, the presence of neutral red in the absence of bile is significant only if the absence of tryptic ferment has been established In brief, the possibility of an extragastric origin of neutral red in the aspirated specimen has to be eliminated to make this test reliable

The estimation of the inorganic chlorides of extracted gastric specimens has been advocated as a more reliable index of gastric acidity Bolton and Goodhart⁷ and Hayem and Winters⁸ affirmed that by ascertaining simultaneously the variations in acidity and sodium chloride of the extracted specimens, during digestion, the effect of intestinal regurgitation on the gastric acid should be definitely seen When the amount of acid remained high for some time, the sodium chloride remained low, when the sodium chloride was high, the acid was comparatively low From these observations it appeared obvious that the concentration of acid in the stomach does not necessarily afford any indication as to whether an excessive or a diminished secretion is present In short, the curve of acidity does not necessarily indicate the secretory activity of the stomach, the only real measure of the amount

5 Piersol, G, Bockus, H, and Banks, J Am J M Sc **170** 405 (Sept) 1925

6 Medes, G, and Wright, C B J Clin Investigation **6** 403 (Dec) 1928

7 Bolton, C, and Goodhart, G W Lancet **1** 420 (March 4) 1922

8 Hayem and Winters, quoted by Rehfus Diagnosis and Treatment of Diseases of the Stomach, Philadelphia, W B Saunders Company, 1927

of gastric acid produced is the cuive of total chlorides, for this includes the hydrochloric acid present as such, as well as the fraction of hydrochloric acid that has been changed into inorganic chloride

Gorham, Stroud and Huffman⁹ carried out a comparative study of the total chloride concentration in a series of cases presenting both normal and abnormal conditions. These authors concluded that estimations of total chlorides in gastric contents are not necessarily a volumetric index to the production of hydrochloric acid by the gastric glands. During their investigation it was found that the chloride concentration of the duodenal contents obtained by means of the tube and of the bile taken from the common duct and of the gallbladder at operation was as high or higher than that of the contents of the stomach. Therefore, the regurgitation of the intestinal fluids into the stomach is in some instances an important factor in determining the height of the chloride level in the gastric contents. An appreciable error would therefore be introduced if chloride estimations should serve as an index of gastric acidity, particularly in cases in which intestinal regurgitation is frequently marked, as in patients with partial gastrectomies. The technical difficulties of such determinations for routine clinical analysis is apparent.

Histamine has been recognized as the most reliable gastric stimulant for hydrochloric acid by numerous workers, particularly Gompertz and Vorhaus¹⁰ and Andresen¹¹. The histamine test for gastric secretion more recently discussed by Bloomfield and Polland¹² embodies not only a study of the degree of acidity, but also the volumetric estimations of gastric secretions. We feel that the volumetric estimation of gastric secretions as advocated in their method is always endangered by the possibility of duodenal regurgitation. That this is not infrequent has been shown in the work of Medes and Wright⁶. Since we have frequently found bile present in the gastric extractions from patients with partial or subtotal gastrectomies, whom we are especially interested in studying, we consider the volumetric estimations by the method of Bloomfield and Polland to be unpractical.

In brief, our survey of the various direct tests for estimating gastric acidity showed certain disadvantages and not entirely controllable factors. We therefore considered employing one of the indirect methods advocated by previous investigators.

9 Gorham, F, Stroud, C, and Huffman, M. Total Chloride Concentration and Acidity of Gastric Contents, Comparative Study, *Arch Int Med* **42** 106 (July) 1928

10 Gompertz, L. M., and Vorhaus, M. G. *Lab & Clin Med* **11** 14 (Oct) 1925

11 Andresen, A. F. R. *Tr Am Gastro-Enterol A*, 1926, p. 53

12 Bloomfield, A. L., and Polland, W. S. Diagnostic Value of Studies of Secretion, *J A M A* **92** 1508 (May 4) 1929

INDIRECT METHOD

Kauders and Poiges¹³ and Lewin¹⁴ described an indirect test for gastric acidity based on the determination of the carbon dioxide tension of the expired air. This method was advocated in cases in which passage of a gastric tube was not feasible. The alveolar carbon dioxide tension expresses changes in the acid base equilibrium, because there are relations in the blood between the carbon dioxide, bicarbonate and phosphates, on the one hand, and the rest of the buffering substances, on the other. The production of acids in the stomach after a test meal suddenly deprives the blood of large amounts of chlorine ions. Consequently, the residual sodium combines with part of the free carbonic acid to form bicarbonate which increases the combined alkali. This would endanger the neutrality of the blood. In order to maintain the neutrality, free carbonic acid is retained so that the ratio of carbon dioxide to sodium bicarbonate remains unchanged in value, the numerator and the denominator being equally increased. In other words, the carbon dioxide tension of the expired air is increased when hydrochloric acid is excreted into the stomach. In such examinations, certain sources of error have to be considered. Even in calm persons, the carbon dioxide tension normally oscillates. Even during sleep there is a definite change in tension. Therefore, any activity during the test must be avoided. Great care must be taken that the patients breathe correctly into the apparatus. These authors found an increase in carbon dioxide tension after a meal test in cases of hyperacidity and no such increase in cases of anacidity. In brief, they showed that the secretion of hydrochloric acid into the stomach plays a principal rôle in the rise of the carbon dioxide tension of the expired air after a test meal. Proof of this lies in the fact that there is essentially no such rise in cases of anacidity. The unavoidable errors and difficulties in carrying out this method make its clinical application impracticable. The important information gained by direct examination of gastric contents is lost in all indirect methods of gastric analysis.

COMBINED METHOD

Since it has been shown by Hubbard, Munford and Allen¹⁵ and by Baehr,¹⁶ Davies¹⁷ and others that persons having relatively normal gas-

13 Kauders, F, and Porges, O. *Deutsche med Wchnschr* **47** 1415 (Nov) 1921

14 Lewin, B. *Deutsche med Wchnschr* **52** 1427 (Aug) 1926

15 Hubbard, R S, Munford, S A, and Allen, F G. *Am J Physiol* **68** 207, 1924

16 Baehr, G. *Bull New York Acad Med* **3** 419, 1927

17 Davies, D T. *Brit J Exper Path* **10** 1 (Feb) 1929

tric secretion are prone to have less acid urine after meals, a phenomenon commonly referred to as the "alkaline tide," it occurred to us that this principle could be incorporated into a test for gastric secretion. These authors have shown the relative fixation of the urinary reaction in cases of achlorhydria.

Ackman¹⁸ was particularly interested in studying the relation between the gastric acidity and the hydrogen ion concentration of the urine after the injection of histamine. He showed that in cases of achlorhydria the alkaline tide is for the most part wanting, and that when histamine, given subcutaneously to a person with normal or high gastric acidity, increases the gastric secretion, it produces a well marked alkaline tide. In cases of hypochlorhydria and in certain cases of achlorhydria in which the secretion of hydrochloric acid is stimulated by histamine, there develops an alkaline tide where formerly there was none. In those cases of achlorhydria in which there is no response to histamine, the alkaline tide fails to develop, apparently owing to a lack of response on the part of the gastric secretion. The absence of any change of the hydrogen ion concentration of the urine in these cases conclusively rules out the possibility that the reaction in other cases might be due to the increased metabolic activity consequent to the injection of histamine. He concluded that the foregoing observation offered strong evidence in support of the gastric origin of the alkaline tide in that in practically all cases a definite relationship between the gastric secretion and the hydrogen ion concentration of the urine has been demonstrated.

It occurred to us to employ this principle of the relationship between the gastric acidity and the urinary acidity (p_H) with histamine as a stimulant in a clinical gastric secretory test. We believed that regardless of the factors that tend to alter the gastric titration values, the simultaneous estimation of the hydrogen ion concentration of the urine would furnish better controlled results. We were able to demonstrate a definite urinary alkaline tide in only about 50 per cent of our patients who developed free hydrochloric acid after the injection¹⁹ of histamine. It is possible that Ackman obtained a greater percentage of urinary alkaline tides after the injection of histamine because his patients received breakfast, apparently, prior to the tests. We have therefore decided that histamine is not the ideal gastric stimulant for use in studies of the urinary alkaline tide. At present, we are experimenting with other test meals. We believe that the combined test of a simultaneous analysis of gastric contents and estimation of urinary acidity (alkaline tide) will give more controlled results.

18 Ackman, F. D. *Canad. M. A. J.* **15** 1099, 1925.

19 This work is to be reported in a subsequent paper.

SUMMARY

1 Various direct and indirect tests for the study of gastric acidity are discussed

2 Histamine should always be employed as a gastric stimulant in cases in which the routine test meal has elicited no response of free hydrochloric acid

3 A definite urinary alkaline tide was found in about 50 per cent of our cases in which free hydrochloric acid was demonstrated after the injection of histamine

4 The advantages of a test combining analysis of the gastric contents with estimation of the urinary acidity (alkaline tide) are discussed

THE ELECTROCARDIOGRAM IN OBESITY^{*}

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It is known that the electrocardiogram undergoes certain changes when the position of the heart in the chest is altered. Einthoven¹ demonstrated that this change took place when the body was rotated from side to side. He showed also that breathing affected the form of the electrocardiogram as it changed the position of the heart, the more transverse position at the end of expiration being associated with more of a left axis, or a tendency in that direction, while at the end of inspiration the axis shifted in the opposite direction. Cohn² demonstrated that there is a rather definite relation between the anatomic angle of the heart as measured on the roentgenogram and the electrical angle as derived from the electrocardiogram. In other words, as the position of the heart becomes more transverse, the electrocardiogram shows a gradually increasing left axis deviation, and as the position becomes more vertical the axis deviation tends to change to the right.

On the basis of these observations it seems logical that in obese people, in whom the diaphragm is usually pushed up so that the heart lies in a comparatively transverse position, there would be a tendency to the production of left axis deviation as measured by the Q R S wave and of associated changes in the T wave.

In a study of the electrocardiogram of ninety-seven obese people, Master and Oppenheimer³ found that 86 per cent showed left axis deviation. They found also that changes in the P and T waves of lead III occurred in 70 and 87 per cent, respectively, of these ninety-seven cases. However, 67 per cent of this group had hypertension, and 85 per cent were reported to have roentgenologic evidence of left ventricular hypertrophy, so that it is difficult to ascertain whether the electrocardiographic changes were due to changes in the position resulting

^{*} Submitted for publication, July 21, 1930.

¹ From the Medical Clinic of the Boston Dispensary, service of Dr. Joseph H. Pratt and the Division of Research.

1. Einthoven, W., Fahr, G., and de Waart, A. Ueber die Richtung und die manifeste Grösse der Potentialschwankungen in menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, *Arch. f. d. ges. Physiol.* **150**: 275 (March) 1913.

2. Cohn, A. E., and Raisbeck, M. J. An Investigation of the Relation of the Position of the Heart to the Electrocardiogram, *Heart* **9**: 311 (Dec.) 1922.

3. Master, A. M., and Oppenheimer, E. T. A Study of Obesity, *J. A. M. A.* **92**: 1652 (May 18) 1929.

from the obesity or to the hypertension and hypertrophy. The correlation of left axis deviation with hypertension, particularly in those cases that present some cardiac enlargement, is fairly definite.⁴ The changes in the T wave may have been merely part of the picture of the left axis deviation, since it is known that the T wave normally bears some relation to the Q R S wave and tends to vary with variations in the amplitude of this initial ventricular phase. Thus an inverted T wave in lead III may be seen in left axis deviation associated with the inverted Q R S complex in the same lead.

It appears worth while to establish more definitely the characteristics of the electrocardiogram in the obese and to point out the common variations from the strictly normal. While these variations may not be definitely abnormal, they are still deviations that are worthy of consideration.

In the present study the cases were separated into two groups (1) those cases of obesity in which the heart was considered normal, and (2) those cases showing hypertension (a systolic blood pressure of more than 170 mm. of mercury), roentgenologic evidence of cardiac enlargement or other cardiac abnormalities. One hundred cases were studied. The electrocardiograms were taken with the patient in the sitting position, with tight clothing loosened, as Romberg⁵ has shown that tight corsets may definitely change the position of the heart. Orthodiagrams were made in the erect position within one week of the electrocardiographic examination. The diagnosis of cardiac enlargement was based on these orthodiagraphic observations, Otten's tables being used as standards.⁶ From the orthodiagram the anatomic angle of the heart was obtained and compared with the electrical angle calculated according to Einthoven¹ from the electrocardiogram. The anatomic angle was taken as that angle which is formed by a horizontal line and a line drawn from the junction of the curve of the right auricle in the orthodiagram with that of the superior vena cava to the apex of the heart. The approximate duration of the obesity as well as the percentage of overweight according to the standard tables of the Metropolitan Life Insurance Company were both recorded as being of possible significance.

4 Proger, S. H., and Davis, D. The Significance of Axis Deviation in the Human Electrocardiogram, *Arch. Int. Med.* **45** 974 (June) 1930. White, P. D., and Burwell, C. S. The Effects of Mitral Stenosis, Pulmonic Stenosis, Aortic Regurgitation and Hypertension on the Electrocardiogram, *Arch. Int. Med.* **34** 529 (Oct.) 1924. Master, A. M. Characteristic Electrocardiograms and Roentgenograms in Arterial Hypertension, *Am. Heart J.* **4** 291 (Feb.) 1930.

5 Romberg, E. Das Herz bei Fettleibigkeit, *Klin. Wchnschr.* **42** 125 (Oct. 15) 1927.

6 Otten, M. Die Bedeutung der Orthodiagraphie für die Erkennung des beginnenden Herzweiterung, *Deutsches Arch. f. klin. Med.* **105** 370, 1911.

ANALYSIS OF CASES

Uncomplicated Obesity—Those cases are considered uncomplicated or cases of simple obesity in which the physical examination of the heart gives negative results, the orthodiagram shows no enlargement or abnormal contour, and the blood pressure is not elevated. Fifty-five are included in this group.

Of these 55, 39 (71 per cent) appeared on simple inspection to have some degree of left axis deviation, that is, exaggeration of the R wave in lead I and the S wave in lead III. By actual measurement of the index and angle, it was found that 31 (56 per cent) showed definite evidence of left axis deviation (angle below 0 degrees or index above +20). In 40 of the 55 cases the electrical angle was below 20 degrees and in 28 it was below 0 degrees, which is taken by many as the lower limit of normal.⁷ Thirty-two of the 55 showed an index over +15, and 20 (36 per cent) showed an index of over +20, which is considered by White⁸ to indicate definite left axis deviation. This high incidence (36 per cent) of axis deviation beyond +20 in cases of simple obesity is a distinct contrast to the 0.5 per cent incidence of such an axis in 1,812 adults without disease of the heart reported by Ferguson and O'Connell.⁹ The average angle of the entire group was 7 degrees, the average index, +16.

Thirty-nine of the fifty-five cases showed an inverted T wave in lead III, and twenty-four exhibited changes in the P wave in lead III (flat or inverted). In studying the electrocardiograms showing inversion of T3 an interesting correlation was observed. It appeared that inversion of T3 was a fairly constant concomitant of left axis deviation when the deviation was thought to be due to change in position. Thirty-one of the cases of simple obesity showed definite left axis deviation, apparently due merely to change in position. Twenty-eight of them showed an inversion of T3. In order to test the validity of this observation, I reviewed the records of thirty-one persons of average size

7 Carter, E. P., Richter, C. P., and Greene, C. H. A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram, *Bull. Johns Hopkins Hosp.* **30** 162 (June) 1919. Dieuaide, F. R. The Determination and Significance of the Electrical Axis of the Human Heart, *Arch. Int. Med.* **27** 558 (May) 1921.

8 White (footnote 4, second reference).

9 Ferguson, D., and O'Connell, J. T. Cardiovascular Observations, Including a Series of Electrocardiograms of Eighteen Hundred and Twelve Men Without Heart Symptoms, *U. S. Nav. M. Bull.* **24** 860 (Oct.) 1926. This incidence of 36 per cent in our cases was decreased, however, by 22 per cent when electrocardiograms were made at the same time of the patients in the lying position.

who showed left axis deviation associated with hypertension (systolic blood pressure over 170 mm of mercury and roentgenologic evidence of cardiac enlargement. Cases showing inversion of the T wave in lead I or II or abnormal spreading of the QRS complex were not included. Only six of these thirty-one showed an inversion of the T wave in lead III (in six of the cases T3 was iso-electric and in nineteen erect), in contradistinction to twenty-eight of thirty-one in the former group. In the latter group one is dealing with cases clinically associated with left ventricular hypertrophy,¹⁰ so that it is reasonable to suppose that in this group the axis deviation in most of the cases is the direct result of the hypertrophy. The figures then indicate that left axis deviation due to change in position is usually associated with inversion of the T wave in Lead III, whereas left axis deviation due to relative left ventricular hypertrophy is commonly associated with an erect T wave in lead III.

There was no significant change in the T wave in leads I and II in any of the cases of simple obesity, even though the axis deviation was considerable in a fair percentage of the cases. This is interesting because, as Cohn² has shown, in the production of axis deviation experimentally by rotating the leads around a large triangle laid out on the chest, thus simulating rotation of the heart on its A-P axis, the T waves change with the QRS waves, and as the QRS waves become inverted and deepen, the T waves also become inverted. Experimentally this occurs in all of the leads. White¹¹ expressed the belief that although inversion of the T wave in lead I or in leads I and II does not occur in a normal heart, it may be the result of marked left axis deviation without disease of the coronary arteries or bundle branch. Such left axis deviation with inversion of the T waves in lead I or II has been found by White to be associated with left ventricular hypertrophy and dilatation (with extension of the bundle branch as well as increase in muscle mass). If with only slight left axis deviation the T wave is inverted in lead I or II, White held that some other factor, such as blocking the left bundle branch, cardiac infarction or myxedema is present. In this study only in lead III did the T wave become inverted as a result of the deviation.

Obesity with Complications—There were forty cases of obesity with cardiac complications and five cases with essential hypertension without demonstrable cardiac involvement. Twenty patients had hypertension and cardiac enlargement. Thirteen of these (65 per cent) showed an angle of less than 0 degrees or an index over +20 (definite left axis

10 Lewis, T. Observations on Ventricular Hypertrophy with Especial Reference to Preponderance of One or Other Chamber, *Heart* 5 367, 1913

11 White, P. D. Personal communication

deviation) The average angle was 6 degrees, the average index, +21 Only five of this group showed inversion of the T wave in lead III, while three showed inversion of the T wave in leads I and II, and one inversion of the T wave in lead I alone Four showed P wave changes in lead III There were five cases of hypertension without cardiac enlargement Of these, three showed left axis deviation, two, inversion of the T and P waves in lead III, and one, inversion of only the T wave in lead III There were nineteen cases of enlargement that appeared on the orthodiagram to be chiefly left ventricular, but without hypertension at the time the picture was taken Of these, eleven showed left axis deviation, ten inversion of T3, and seven changes in P3 The average angle of this group was 8 degrees, the average index, +19 There was one case of rheumatic mitral stenosis that showed a normal angle and index, but in which a diphasic T wave in lead II and an inverted T wave in lead III were recorded The orthodiagram in this case showed a distinct right-sided enlargement

The electrical axis did not differ materially whether or not the heart was involved For example, the average angle in the group with simple obesity was 7 degrees and the average index +17, while in the group with hypertension and cardiac hypertrophy the averages were 6 degrees and +21, respectively Fifty-six per cent of the cases of simple obesity showed definite left axis deviation, while 65 per cent of the cases of obesity with hypertension and cardiac hypertrophy showed such an axis It is known that in people of ordinary size there is a definitely greater incidence of left axis deviation in those with hypertension and cardiac hypertrophy than in those with no cardiac abnormalities,⁴ so that axis deviation is considered by many to be of some value in the diagnosis of relative ventricular hypertrophy¹² In the obese, however, left axis deviation appears almost to the same degree and as frequently in cases of simple obesity as in cases with hypertension and cardiac hypertrophy Thus changes in the axis that may be produced by left ventricular hypertrophy are obscured by the changes associated with obesity Therefore, deviation of the axis is probably of no significance in the obese Although inversions of the T wave in leads I and II theoretically may be associated with marked deviations in the electrical axis, in this study they are found not to occur in those cases in which the heart is apparently normal, despite marked deviation of the axis In the four cases in

12 Pardee, H E B Determination of Ventricular Preponderance from the Electrocardiograph, *Arch Int Med* **25** 638 (June) 1920 White, P D, and Bock, A V Electrocardiographic Evidence of Abnormal Ventricular Preponderance and of Auricular Hypertrophy, *Am J M Sc* **156** 17 (July) 1918 White (footnote 11) Carter (footnote 7, first reference)

which these inversions were associated with marked left axis deviation, there is definite clinical evidence of myocardial disease

Comparison of Electrical and Anatomic Angle—Since it is true that the changes in the electrocardiogram of the obese seem to be due to the changes in position resulting from the obesity rather than to any direct cardiac effect, it appeared advisable to compare the anatomic and electrical angles and to determine if possible whether or not the usual transverse position of the heart in obesity with its low anatomic angle is paralleled by changes in the electrical angle

There does appear to be a general relationship between the anatomic angle of the heart as measured with a protractor ~~on the cardiogram~~ and the electrical angle as calculated from the electrocardiogram. Of the twenty-five cases in the entire group in which the anatomic angle was below 30 degrees and in which the heart may be said to have been in a more or less transverse position, the average electrical angle was 1 degree, which may reasonably be considered as left axis deviation. Of eleven cases in which the heart was more oblique, the anatomic angle being over 40 degrees, the average electrical angle was 28 degrees, which may be considered normal. A similar comparison in the group with normal hearts shows that the average electrical angle was 1 degree in those cases in which the anatomic angle was below 30 degrees, while it was 20 degrees in those cases in which the anatomic angle was above 40 degrees. In the group with simple obesity there were thirty-two cases with the anatomic angle below 35 degrees. The average electrical angle of these cases was 2 degrees, the electrical angle in none being over 25 degrees. There were twenty-three cases of simple obesity in which the anatomic angle was more than 34 degrees (from 35 degrees to 47 degrees). The average electrical angle in this group was 17 degrees, and only two cases showed an electrical angle below 0 degrees, or definite left axis deviation. It is fair to conclude from these figures that the variations in the anatomic angle that occur with rotation of the heart on a horizontal axis usually are associated with corresponding changes in the electrical angle of the heart. The important influence on the electrocardiogram of rotation of the heart on a vertical axis,¹³ which cannot be ascertained in a study such as this, may well account for the discrepancies noted.

Influence of Age, Sex, Percentage of Overweight and Duration of Obesity—The average percentage of overweight was 33. The percentage of overweight beyond approximately 25 in the individual cases

13 Meek, W. J., and Wilson, A. The Effect of Changes in Position of the Heart on the Q R S Complex of the Electrocardiogram, *Arch Int Med* **36** 614 (Nov) 1925

seemed to have no direct bearing on the electrocardiographic changes. The age was likewise found to have no effect in the cases studied, in which all of the patients were adults. For example, in the twenty-two cases of simple obesity in persons between the ages of 20 and 40, the average angle was 7 degrees and the average index $+15$, while in thirty cases of simple obesity in persons between the ages from 40 to 60, the average angle was 8 degrees and the average index $+16$. The duration of the obesity was in no way related to variations in the electrocardiogram in the normal group, nor did the sex appear to be an influencing factor.

SUMMARY AND CONCLUSIONS

1 The electrocardiogram of the obese person with an apparently normal heart in a large percentage of cases shows left axis deviation, flattening or inversion of the P wave and inversion of the T wave in lead III.

2 In those cases in which the heart appears to be normal, there are no significant changes in the T wave in leads I and II, regardless of the extent of the axis deviation.

3 Left axis deviation due to change in position is usually associated with inversion of the T wave in lead III, whereas left axis deviation owing to relative left ventricular hypertrophy is commonly associated with an erect T wave in lead III.

4 Cases of obesity without other organic disease show approximately the same incidence and extent of left axis deviation as cases of obesity complicated by hypertension and cardiac enlargement.

5 Axis deviation in the electrocardiogram of the obese patient is of no value as an aid in the diagnosis of relative ventricular hypertrophy.

6 There appears to be a general relationship between the anatomic angle of the heart as measured on the orthodiagram and the electrical angle as calculated from the electrocardiogram.

7 Factors such as age, sex, duration and percentage of overweight beyond 25 per cent seem to have no definite relation to changes in the electrocardiogram.

HYPOCHROMIC ANEMIA WITH ACHLORHYDRIA¹

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In contrast to hyperchromic anemia with achlorhydria, commonly called pernicious anemia, hypochromic anemia with achlorhydria has received comparatively little attention. This is due principally, it would seem, to three factors. 1. This type of anemia is so readily confused with other hypochromic anemias that it often is not recognized. Many physicians are satisfied to rule out pernicious anemia carefully and then to rest content on a diagnosis of "secondary anemia" without further investigation or distinction. A smear is made, a blood count is done, no megalocytes are found, the color index is low, and at once all interest in the anemia disappears. 2. This condition never reaches the severity of pernicious anemia, and hence is more readily passed over. The patients do not look as sick as they really are, and one is greatly surprised to find the hemoglobin so low. They show so favorable a picture on physical examination, except for the anemia, and they complain so little except of fatigue, lassitude and perhaps palpitation on exertion that one is inclined to consider them hypochondriac. Moreover, although the anemia is persistent, it rarely, if ever, increases to a sufficient degree to cause the death of the patient. While this lack of a possible fatal outcome cannot but lessen concern, it in no way alters the economic importance of the condition. 3. The disease has never received the attention in the literature that it would seem to deserve. It has never stood out as a clearcut entity, but has been treated as a sort of side issue in the discussion of achlorhydria and its relation to pernicious anemia. Thus its own detail has been more or less lost in theoretical explanations of pernicious anemia.

Although the condition had been recognized for some time, Faber¹ in his address before the International Congress of Medicine in London, in 1913, drew attention to the fact that not only pernicious anemia, but a simple chlorotic type of anemia might occur, associated with gastric

¹ Submitted for publication, Aug 11, 1930

² Read in preliminary form before the Osler Reporting Society, Montreal, Jan 24, 1930

³ From the Department of Haematopathology of the Pathological Institute, McGill University and the Royal Victoria Hospital

1. Faber, K. Anämische Zustände bei der chronischen Achylia gastrica, Berl klin Wchnschr 50 958, 1913. Faber, K., and Gram, H. C. Relations Between Gastric Achylia and Simple and Pernicious Anemia, Arch Int Med 34 658 (Nov) 1924

achylia He described a case and pointed out that 15 of 207 uncomplicated cases of achylia showed percentages of hemoglobin below 50 At this time he considered that the achylia predisposed to the production of hemolytic toxins of bacterial origin in the intestine, which were the direct cause of pernicious anemia Later further statistics were published, and the theory arose that congenital predisposition is the deciding factor as to whether in achlorhydria a hypochromic or hyperchromic type of anemia should arise In 1929, Altschuller² reported a similar case, reviewed the work of Faber, and drew the conclusion that the achlorhydria is not the preponderant or exclusive cause of the anemia, but rather the expression of an abnormal constitution in which this type of anemia may develop According to his views, as Naegeli thought for chlorosis, the real cause lies deeply buried in a disturbance of the complex regulatory mechanism of hematopoiesis

Watkins,³ in his recent classification of what he refers to as chronic idiopathic anemia, includes as his third group an anemia of middle-aged women, which agrees in many respects with the condition under discussion He stated, however, that achlorhydria may or may not be present, and apparently, therefore, did not consider this of primary importance in the disease picture

Witts,⁴ in an article on the relation of achlorhydria to anemia, recently called attention to this simple (hypochromic) form in contrast to pernicious anemia He stated that in his experience it is even more common in patients with achlorhydria than pernicious anemia, and, for the reasons that we have already pointed out, is often not recognized In his opinion achlorhydria, or at least marked hypochlorhydria, is always present and plays a primary rôle in the pathogenesis of the condition, although the finer details of the mechanism of this development are still in doubt

In the course of several hundred complete morphologic examinations of the blood, I encountered this condition on several occasions At first comparatively little attention was paid to it, but as the finer diagnostic features of the blood picture became clearer and a prediction of achlorhydria was often possible before gastric analysis was done, my interest in it became aroused It then took the appearance of a disease entity Moreover, as time goes on, more and more cases appear, so one cannot but feel that either the condition is becoming more common or many

² Altschuller, G Sur la pathogenie de l'anemie hypochrome chronique, dite achylique *Acta med Scandinav* **70** 119, 1929

³ Watkins, C H A Classification of Chronic Idiopathic Secondary Anemia With Especial Reference to the Morphology of the Blood, *J A M A* **93** 1365 (Nov 2) 1929

⁴ Witts, L J Achlorhydria and Anaemia, *Practitioner* **124** 348 (March) 1930

cases have gone unrecognized in the past. If such is the case, it would seem worthy of much more detailed study than it has received. I shall, therefore, summarize the outstanding clinical and hematologic features of my cases as a whole, give a more detailed history in some individual cases and discuss briefly the possible nature of the disease and its claim to an entity.

CLINICAL FEATURES

All of the cases that I have encountered have occurred in women. Cases have been reported, however, in men, though the great preponderance in women is a well recognized fact. Most of the women are from 35 to 45 years of age, though occasional cases in younger and slightly older women occur. None of my cases occurred in a woman after the menopause.

These women give a history of a healthy childhood and adolescence. Careful questioning as to anemia coming on at puberty or any evidence of a chlorotic diathesis at this time was generally answered by the statement that they were healthy with good color. One finds, however, in the history of the later years two outstanding features: (1) often indefinite stomach trouble with possibly an operation for ulcer and (2) always a persistent anemia and general weakness and lassitude. Many of the patients have had several children and have noted that during pregnancy they were particularly weak and compelled to spend the later months in bed. Several of the patients were examined because of indefinite anemia during pregnancy, but careful questioning brought out the fact that the anemia was probably present before pregnancy began.

Physically, these women are generally slender, with conspicuous musculature. They do not appear to have aged unduly. They are not apparently very sick, but are pale, weak, tired and unanimated, often with a quiet attitude of mind suggesting resignation to their fate. They may complain of shortness of breath or palpitation on exertion. Often they report dyspepsia, and they are extraordinarily careful about their diet and choice of food.

Physical examination reveals comparatively few abnormal signs. There may be a faint systolic murmur, and the blood pressure is inclined to be low. There is no appreciable splenic or glandular enlargement. Careful examination of the stools shows no evidence of loss of blood. Moreover, there is rarely a history of excessive bleeding at menstruation, though occasionally menorrhagia is the initial symptom of an exacerbation. All efforts to explain the anemia on a posthemorrhagic basis fail. Gastric analysis, however, reveals an absence of free hydrochloric acid after the test meal, and I am inclined to believe that this or at least extreme hypochlorhydria, is a constant observation. The blood picture, moreover, is quite typical and will be taken up here in detail.

MORPHOLOGIC DETERMINATIONS OF THE BLOOD

The red blood cells are only moderately reduced in number, figures between 3,500,000 and 4,000,000 being most common. On the other hand, the hemoglobin is relatively low, ranging from 30 to 60 per cent. Consequently, the color index is often extremely low, and the hemoglobin concentration is markedly reduced. The cells are pale and stain poorly and irregularly. Morphologically, they vary considerably in size, with occasional forms larger than normal and the great majority much smaller, figures for the average volume of corpuscles from 60 to 70 cubic microns are common. Poikilocytosis and polychromatophilia vary from slight to moderate. Punctate basophilia has not been observed, and nucleated red cells do not occur except in severe and possibly complicated cases. Not over 2 per cent of the cells show reticulations with the so-called vital stain. On macroscopic examination, the fragility appears comparatively normal, however, by the microscopic method described by Chase and myself⁵ anisohemolysis is demonstrable, and the peculiar combination of increased resistance in the lower tubes and increased fragility in the higher concentrations is present. This is met with in other types of hypochromic anemia. The sedimentation velocity is remarkably slow considering the severity of the anemia, and stands in distinct contrast to that in pernicious anemia in this respect. Readings indicative of a velocity only slightly above the normal are the rule.

In typical cases there are from 4,000 to 5,000 white blood cells per cubic millimeter, that is, a moderate leukopenia. This is due primarily to a definite reduction in neutrophil polymorphonuclears. The monocytes are also actually reduced in number, although their percentage may be slightly increased. There is often a relative, but never an absolute, lymphocytosis, and these forms may also be reduced in number. In many cases of hypochromic anemia the mast cells may be noticeably increased, and occasionally there is slight eosinophilia. The polymorphonuclears do not exhibit toxic changes, but there is often increase lobation of the nuclei, that is, a shifting of the index of nuclear segmentation to the right as in pernicious anemia. Immature forms, such as myelocytes, are but rarely seen in typical cases.

The platelets are somewhat reduced in number, though low figures suggesting an approaching hemorrhagic diathesis were not observed. There is no prolongation of the bleeding time. As regards coagulation, fibrin formation appears to occur more rapidly than normally in the majority of cases, and congealing of the blood both without and in the

5 Waugh, T. R., and Chase, W. H. A Combined Macroscopic and Microscopic Erythrocyte Fragility Technic, *J. Lab. & Clin. Med.* **13** 872 (June) 1928.

presence of added calcium chloride tends to be somewhat shortened. Retraction of the clot occurs promptly and to a marked degree.

Finally, the serum is inclined to be a rather pale yellow with a faint or moderate green tinge. Refraction of the plasma ranges from 55 to 59 with the dipping refractometer. The van den Bergh reaction never shows a marked bilirubinemia. The prompt direct reaction is negative and the delayed direct reaction, as a rule, faint. By the indirect method most cases give less than 0.3 units of bilirubin, but occasionally slightly higher figures, though within normal limits, are found.

To summarize, there is a marked low color index, i. e., hypochromic anemia, with evidence of deficient erythropoietic and leukopoietic myeloid activity. Moreover, the anemia is not hemolytic.

In severe cases, as occasionally occurring in women during pregnancy, the foregoing picture may be somewhat altered. The anemia is more marked and nucleated red cells and myelocytes appear, but the blood picture as a whole maintains the same essential characteristics.

COURSE AND RESULTS OF THERAPY

The anemia in these cases is extraordinarily persistent. Following pregnancy, there is apparently some improvement, but a marked anemia persists. The patients invariably complain that they dislike taking iron and that it does them no good. Arsenic possibly causes an improvement in the subjective symptoms but no appreciable alteration in the blood picture. These cases do not respond to liver therapy as do those of pernicious anemia. I have examined two cases in particular after a long-continued diet of liver and found no appreciable alteration in the blood. The benefit of transfusion is only temporary, and the blood rapidly falls to its previous level. In fact, the persistence of the anemia and its tendency to maintain a constant level for months in spite of all manner of therapy is one of the outstanding characteristics of the disease. One patient whom I have examined on numerous occasions for over two years, during which time she was treated by all the recognized methods of stimulating the formation of the blood, even by splenectomy, has maintained constantly approximately 4,000,000 red cells and 45 per cent hemoglobin.

Other authors have obtained much greater improvement in these cases under iron therapy than my results would indicate. They all emphasize, however, the necessity of giving the drug in large doses.

I have had no experience with the beneficial effect of a powder prepared from the fetal liver of calves, as described by Watkins. Recently, however, I have had the opportunity to follow the effects of iron and copper therapy, as advocated by Mills⁶. In one particularly persistent

6 Mills, E. S. The Treatment of Idiopathic (Hypochromic) Anaemia with Iron and Copper, *Canad. M. A. J.* **22**: 175 (Feb.) 1930.

case, which had been under observation for several years during which time it had never shown a hemoglobin percentage over 60 per cent, there occurred a distinct rise to 76 per cent, and an improvement in the color and general appearance of the patient, but no appreciable amelioration of subjective symptoms. As this case was carefully followed and never showed the least response to the usual forms of treatment for anemia, I am inclined to the view that there is a more or less specific therapeutic value in the combination of copper with the iron in the treatment for this condition.

While I have been able to follow up only a few of these patients after they have left the hospital and only for a comparatively short time, none has completely recovered, but, perhaps even more remarkable, none to my knowledge has died. Unfortunately, therefore, I cannot report on pathologic changes taking place in the body, with the exception of those in the blood.

INCIDENCE

My observations have extended over far too short a time to assert that the condition is becoming more common. Such a fact is most difficult to establish even over long periods. However I am struck, as time goes on, by the increasing number of women whose blood I am asked to examine, who appear to be suffering from this type of anemia. I have not as yet had an opportunity to go over the older records for comparison, but in 1929 six cases were examined which fall definitely into this group, and four more were seen within the first half of the present year.

SUMMARIES OF INDIVIDUAL CASES

CASE 1—History—Mrs. G. O., aged 39, had entered the hospital on several occasions during the past two years. She gave a history of good health through childhood and to the age of 30, when she had influenza. Since then she never completely regained her health. She complained of weakness and of becoming fatigued easily. Menstruation was somewhat irregular, and the flow scanty. She had had three normal pregnancies. Five years before entrance to the hospital she was operated on for an ovarian cyst, and two years later a uterine polyp was removed. She had never been jaundiced. The appetite was good, although she had some gas after meals. Three years before I saw her an examination of the blood was made, and she was told that she had pernicious anemia. She was treated by various methods, including liver therapy, without improvement.

Examination—Since the patient has been under my observation, physical examinations have given essentially negative results. No focus of infection could be demonstrated. The urine and stools were normal. Gastric analysis failed to show free hydrochloric acid either before or after the test meal.

Morphologic examinations of the blood were carried out on several occasions. On Jan. 8, 1929, the first test showed red cells, 4,300,000, white cells, 4,000, hemoglobin, 67 per cent (94 Gm. per hundred cubic centimeters), and color index, 0.78.

The red blood cells showed marked anisochromia, marked anisocytosis with some large and many small forms, moderate poikilocytosis and polychromatophilia, no punctate basophilia or nucleated cells, reticulated cells, 1 per cent, fragility test, anisohemolysis, corpuscle volume, 35 per cent, average corpuscle volume, 81 cubic microns, and hemoglobin concentration, 0.84. There were 4,000 white blood cells, and an examination of 400 showed 2,240 polymorphonuclears per cubic millimeter, or 56 per cent, 40 eosinophils, or 1 per cent, 40 mast cells, or 1 per cent, 390 monocytes, or 9.75 per cent, and 1,290 lymphocytes, or 32.25 per cent. There was a reduction in myeloid elements. The platelets numbered 110,000 and were usual in size and shape. The bleeding time was not appreciably prolonged. The coagulation time for the formation of fibrin was six minutes, congealing, five minutes, and congealing with calcium, nine minutes, clot retraction was present.

The serum was yellow with a faint greenish tinge. The refraction of the plasma was 59. The results of the van den Bergh test were direct, prompt, negative, direct, delayed, faintly positive, and indirect, 0.5 units of bilirubin.

Course—Four subsequent examinations of the blood within the last eighteen months showed almost identical determinations. Various forms of treatment for anemia have been resorted to without change in the blood picture. Recently the patient left Montreal. Her physician advised iron and copper therapy, but I am unable to report the results. In this case the anemia was comparatively mild, but characteristically persistent.

CASE 2—History—Mrs. O., aged 40 entered the hospital on Jan. 20, 1930, for examination and special tests. She complained of loss of strength, palpitation and general malaise. She had been in rather poor health for the past fifteen years, but during the last six months she had noticed increasing lassitude, with palpitation on exertion and loss of color. She had never been jaundiced or noticed bloody, tarry or clay-colored stools. The menstrual periods were irregular and without excessive loss of blood until the past few months, when they were somewhat prolonged, with a slightly increased flow. She had never been pregnant. The personal and family histories were irrelevant, except for the account of several attacks of pleurisy in the past fifteen years.

Examination—Physical examination showed the patient to be moderately well nourished, very pale and of an older appearance than is ordinary for the stated age. She did not appear acutely ill. The temperature was 98.4 F, the pulse rate 85, and the respiratory rate 20. The mucous membranes were pale, and the tongue, red, glazed and fissured. There was no glandular enlargement. The lungs were clear. The blood pressure was 140 systolic and 58 diastolic. There was a systolic murmur. The liver was just palpable, the spleen, however, was not. The urine and stools were normal. The electrocardiogram was normal. The basal metabolic rate was +21.4. A roentgenogram showed the chest to be normal except for calcified glands at each hilus. The gastric analysis did not show free hydrochloric acid before or after the test meal.

The complete morphologic examination of the blood showed red cells, 3,800,000, white cells, 5,200, hemoglobin, 35 per cent (4.9 Gm per hundred cubic centimeters), color index, 0.46.

The red blood cells stained poorly. They showed marked anisocytosis with many small forms, moderate poikilocytosis, slight polychromatophilia, no punctate basophilia or nucleated cells, reticulated cells, not over 1 per cent, fragility test, anisohemolysis, corpuscle volume, 22 per cent, average corpuscle volume, 58 cubic microns, hemoglobin concentration, 0.7, and viscosity, low. The white blood cells

numbered 5,200, an examination of 500 showed 3,422 polymorphonuclears per cubic millimeter, or 66.8 per cent, 31 eosinophils, or 0.6 per cent, 21 mast cells, or 0.4 per cent, 488 monocytes, or 9.4 per cent, and 1,238 lymphocytes, or 23.8 per cent. There was a slight reduction in polymorphonuclears, but no toxic changes. The platelets numbered 210,000 and were usual in size and shape. The bleeding time was not appreciably prolonged. The coagulation time for the formation of fibrin was one-half minute, and for congealing, seven minutes, retraction of the clot was present and marked. The serum was a rather pale yellow with a faint greenish tinge. Refraction of the plasma was 59. The results of the van den Bergh test were direct, prompt, negative, direct, delayed, faintly positive, and indirect, 0.4 units of bilirubin.

Course—The patient left the hospital on January 25, and is being treated in her home. No subsequent examinations have been made on the blood. In this case the grade of anemia was especially severe.

Other cases might be included, particularly those with histories of gastric trouble or cases examined during pregnancy, which vary somewhat from those given. However, as the diagnostic features are essentially the same, they will be omitted.

DISTINCTION FROM OTHER TYPES OF ANEMIA

Several of these cases were sent to me with a possible diagnosis of pernicious anemia for detailed examination of the blood. The diagnosis may have been suggested by the anemia in the presence of achlorhydria or simply by the general appearance of the patient. In one case the diagnosis of pernicious anemia had been settled on definitely, and the patient treated accordingly for several weeks. Failure to improve on a strict diet of liver led to a further investigation.

Complete observations of the blood leave no possibility of confusing the two conditions. There is a great similarity in the differential picture of the white blood cells, however, the marked hypochromic character of the anemia and the lack of bilirubinemia are points of sharp distinction. I appreciate the possibility of having genuine pernicious anemia with a color index below 1, however, in such cases the hemoglobin concentration remains high, and the lowering of the color index is due to the presence of many small fragments of erythrocytes or schizocytes. There seems to be no hematologic grounds for concluding that these cases should be considered atypical cases of pernicious anemia, and certainly their lack of response to liver therapy is against such a conclusion.

That these cases of hypochromic anemia with achlorhydria are not mere cases of secondary anemia in which the etiologic factor is obscured is much more difficult to establish. Posthemorrhagic conditions with poor regenerative ability on the part of the hematopoietic system might give a similar blood picture, however, demonstration of the loss of blood completely fails, and the maintenance of such a constant level of anemia is against such a conclusion.

Similarly such chronic toxic states as tuberculosis or nephritis often show severe cases of hypochromic anemia with poor regenerative ability, the bone marrow is hypoplastic, and the body does not appear to respond to the deficiency in blood. I can say only that there is no evidence up to the present time that such a primary condition plays a role in this disease.

The marked hypochromic character of the anemia and its occurrence in this series in women exclusively, make one think of chlorosis, in this connection several points need to be mentioned. Whether or not a true chlorosis can actually exist in later life has been disputed for some time. Naegeli is the chief supporter of the affirmative view. If late chlorosis does exist, and I am inclined to believe that it does, the term should be employed and the disease defined as a persistence of the chlorotic state into middle life. In other words, the term should be used exclusively for cases having the same general clinical picture and identical blood pictures of typical chlorosis, and only in those cases which meet all specifications of that disease. The term should not be loosely employed to designate any case of idiopathic anemia with low color index in middle life.

In the hypochromic anemia that I am discussing, the history and constitutional make-up of chlorosis are lacking. As a rule, my patients gave a history of a healthy girlhood. Moreover, in contrast to the frequent sterility of chlorotic patients, these patients are often prolific. The blood picture has certain points of similarity, particularly the erythrocyte changes, however, the changes are not specific of chlorosis, but are met with in any severe case of hypochromic anemia. The usual platelet increase of chlorosis is lacking, and the leukopenia is persistent and definite. Finally, while the reports of the analysis of the contents of the stomach in chlorosis give various results, hyperacidity is most common. All of these facts combine to support a conclusion that, although one is dealing with a chlorotic type of anemia, one is not justified in considering the condition under discussion a variant of that disease. I therefore feel that there are good grounds to support the view that this type of anemia may be looked on as a disease entity.

IS ACHLORHYDRIA ALWAYS PRESENT?

Watkins, in describing his third group of idiopathic secondary anemia, stated that there may or may not be an associated achlorhydria, and apparently he did not consider this a pathognomonic factor of the disease picture. Mills, in the cases which he grouped together under the designation idiopathic hypochromic anemia, stated that achlorhydria is generally present, but may be lacking. In all of my cases there has been a distinct lack of free hydrochloric acid in the contents of the stomach both during fasting and after a test meal. It may be merely a

coincidence that I have not had any cases with a lack of achlorhydria in my series, or it may be possible that achlorhydria develops only late in the disease and that early cases show free hydrochloric acid. I am inclined to believe, however, that achlorhydria, or at least extreme hypochlorhydria, as in pernicious anemia, is a pathognomonic factor of the condition that I have described, and that all cases that do not present it are not to be included in this group. In the two cases in which histamine tests were carried out, no free hydrochloric acid was found in the contents of the stomach following the administration of, at first, one-half and, on a later date, 1 mg subcutaneously. The importance of the question as to whether or not achlorhydria is always present becomes more obvious when one considers various hypotheses as to its nature.

POSSIBLE NATURE OF THE DISEASE

The outstanding feature of this type of anemia is the hypochromic character. A relatively high erythrocyte count with a low hemoglobin percentage is always present. Watkins called attention to this apparently normal ability of the bone marrow to keep up the number of red blood elements while maintaining a marked deficiency in the concentration of hemoglobin. As he stated, there is an apparent dysfunction in the synthesis of hemoglobin. Too, in my cases at least, there has been the constant presence of achlorhydria, which may be either primary or secondary to the anemic state. This question bears considerable weight in constructing theories as to the nature of the disease.

If the achlorhydria is primary, the recent work of Castle and Townsend on the etiologic relationship of achylia gastrica to pernicious anemia may have an important bearing here. These authors showed that by treating patients with pernicious anemia with beef muscle previously incubated with normal gastric juice a progressive improvement in the anemia results comparable to that resulting from liver diet. However, neither of these substances separately produce the beneficial effect. They argue, therefore, that the effective substance is produced by the action of normal gastric juice on the muscle. Liver evidently supplies this effective substance and does not require the action of normal gastric juice to form it. It would seem, therefore, that in such cases of achylia gastrica not only hydrochloric acid but certain proteolytic ferments necessary for the production in the body of the effective substance are lacking.

Returning to the type of hypochromic anemia with achlorhydria under discussion, the possibility is offered that here too one is dealing with a deficiency in gastric activity. This leads to the absence or incomplete formation of some chemical substance which although differing from the effective substance in liver is essential for the maintenance of normal hematopoiesis. Its absence or presence in too small amounts

leads, not to the typical hyperchromic type of anemia met with in pernicious anemia, but rather to hypochromic anemia characterized particularly by persistent deficiency in hemoglobin formation

If, on the other hand, the achlorhydria is simply secondary to, and the result of, the anemia, one must look elsewhere for the primary cause. That achlorhydria may result from anemia has been held for a long time. However, it is difficult to conceive how anemia alone can cause it, and certainly many severe cases of anemia cover long periods without a marked change in the gastric secretions. One should certainly hesitate to explain away the achlorhydria as simply as has been done in the past. Up to the present time none of the cases which I have examined, to my knowledge, has shown any primary etiologic factor such as would warrant its being put into the common category of so-called secondary anemia. Only further observations over long periods of time can rule out this possibility.

Granted, therefore, that the achlorhydria is not purely secondary, there are still the theories of Faber and Altschuller, mentioned before to bear in mind. As regards the former, the same arguments pro and con as to the importance of intestinal flora in pernicious anemia apply here. A massive literature has grown up on this question which it is beyond the scope of this paper to discuss. As regards Altschuller's views, while they may be correct, they are at best disappointing so far as they seem to bury the cause of this type of anemia beyond the means of scientific excavation. I am impressed by the fact, however, that although apparently authentic cases have been described in men, all of my cases have occurred in women, and that this type of anemia is certainly much more common in this sex. Moreover, I have not met with a single typical case in a woman past the menopause. Such facts suggest an endocrine or nervous factor, and I cannot but feel that while similar, the cases occurring in men may eventually be found to be not strictly identical as regards etiology and pathogenesis.

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THE CHOLESTEROL PARTITION OF THE BLOOD PLASMA IN PARENCHYMATOUS DISEASES OF THE LIVER *

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In evaluating the status of diseased organs, certain attempts might be directed to the deviations in the normal functions of synthesis and excretion. In the liver such tests have diagnostic limitations, since the degree of parenchymatous involvement does not necessarily parallel the impairment of the various individual functions, moreover, the process of regeneration in the liver is frequently extensive.

The tolerance tests for levulose and galactose, which have received much attention, have not always been very fruitful in the elucidation of the problem. The results obtained with the dye excretion method are too sensitive, and the presence of jaundice causes errors in the quantitative estimation, moreover, there is some hesitancy in employing this method if the liver is already damaged, especially if there is also marked diminution in the excretion of bile. The study of the biliary pigments in the blood enables one to detect the presence of jaundice before its clinical visibility, but, except for the differentiation of the hemolytic anemias, it offers little aid in connection with the various parenchymatous diseases of the liver, as bilirubin is detected in hemolytic and obstructive jaundice when relatively little damage of the liver has occurred. This objection also holds for the presence of the pigments in the urine. The determinations of lactic acid and amino-acids in the blood and urine are very complicated, and the urea of the blood begins to show abnormal deviations only in extreme damage, since its formation is one of the last of the functions of the liver to disappear.

Experimental and clinical data in recent years have focused attention on the important rôle of the liver in the cholesterol metabolism. According to the majority of authors, there is in the normal blood plasma of human beings from 140 to 200 mg of total cholesterol per hundred cubic centimeters, depending on the method of examination employed, and of this from 50 to 70 per cent is in the form of cholesterol ester (the combination of 1 molecule of free cholesterol with 1 molecule of a

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fatty acid) Among others, Hueck¹ expressed the belief that the greatest source of the cholesterol in the body is exogenous, the enterogenous resorption depending on the amount of cholesterol in the food and on the presence of fatty acids, bile and pancreatic juice in the intestines The main excretory path of the cholesterol is via the bile, and in the human being the cholesterol in the bile is in the form of free cholesterol According to Thannhauser,² the liver is the regulator not only of the cholesterol content of the blood, but also of the relation of the free cholesterol to the cholesterol ester The liver is also its chief excretory organ That other organs, and especially the reticulo-endothelial system, may be involved in the cholesterol metabolism was shown by the work of Rothschild,³ Leites,⁴ Frenckell and Nekludow⁵ and others on the suprarenals, lungs, spleen and other parts of the reticulo-endothelial system

In the liver a reversible reaction of synthesis of cholesterol ester from fatty acids and free cholesterol and of hydrolysis or saponification by means of esterases into free cholesterol and fatty acids is always occurring Kondo⁶ and Schultz⁷ were the first to demonstrate in the liver of horses and cows a ferment capable of splitting cholesterol ester, and to this is attributed the absence of cholesterol ester in the bile Thannhauser demonstrated the presence of esterases in the intestines, in the duodenal and pancreatic juices and in the bile of human beings, and he also believed in the possibility of the saponification of the ester in the intestines

It seemed that a study of the liver might be undertaken with reference to its property of regulating the cholesterol content and the ratio of the free cholesterol to the cholesterol ester in the blood In reporting on the lipoids in acute yellow atrophy, Feigl⁸ noted low figures for the cholesterol ester (from 11 to 50 per cent of the total), but he did not attach any particular significance to these observations Thannhauser and Schaber⁹ showed that in cases of damage of the liver the values for cholesterol ester were below those of the free cholesterol, and that in the more severe cases (acute yellow atrophy) the values for ester were

1 Hueck, W Zentralbl f Path u path Anat **36** 211, 1925

2 Thannhauser, S J Lehrbuch des Stoffwechsels und der Stoffwechselkrankheiten, Munich, J F Bergmann, 1929

3 Rothschild, M A Beitr z path Anat u z allg Path **60** 39, 1915

4 Leites, S Biochem Ztschr **184** 273, 1927

5 Frenckell, G, and Nekludow, V N Arch f d ges Physiol **220** 356, 1928

6 Kondo, K Biochem Ztschr **26** 238, 1910, **27** 436, 1910

7 Schultz, J H Biochem Ztschr **42** 255, 1912

8 Feigl, J Biochem Ztschr **86** 1, 1918

9 Thannhauser, S J, and Schaber, H Klin Wchnschr **5** 252, 1926

so depressed and lowered as to be occasionally entirely lacking, which disappearance Thannhauser called "Estersturz." Enderlen, Thannhauser and Jenke¹⁰ extirpated the liver in 6 dogs, and in only two were they able to demonstrate a fall in the ester cholesterol content of the blood. Adler and Lemmel,¹¹ in a large series of cases of acute and subchronic yellow atrophy and icterus catarrhalis, demonstrated that the lowering of the values for cholesterol ester ran parallel to the severity of the degeneration of the liver, and that with recovery the normal values were gradually reached. In twenty-seven cases of cirrhosis of the liver, little or no changes in the values for the cholesterol ester were found. On the other hand, Burger and Habs¹² in cases of severe damage of the liver in human beings, Rosenthal, Licht and Melchior,¹³ in extirpation of the liver of dogs, and Stein and Suchantke,¹⁴ in clinical and experimental investigations, were not able to corroborate the observations of a complete disappearance of the cholesterol ester. Moreover, Mann¹⁵ found no change in the cholesterol before and at periods following the removal of the liver.

The contradictory results encountered in clinical observations might be obviated if the cases were studied from the onset of the injury until the termination in either recovery or death. The present study comprises the results of such observations in ten cases of acute parenchymatous disease of the liver, of unknown etiology, occurring in the course of infection, following medication, and varying in intensity from mild hepatitis in a case of pneumonia to fatal acute yellow atrophy, and in four cases of atrophic cirrhosis of the liver. The work was done in the chemical laboratory with the supervision of Dr. Harry Sobotka.

Determinations of the total, free and ester cholesterol content of the blood were carried out on from 1 to 2 cc. of blood plasma taken from the patients in the morning before breakfast, the method of Bloor and Knudson¹⁶ was employed. A short summary of the clinical histories and observations in these cases is presented.

10 Enderlen, E., Thannhauser, S. J., and Jenke, M. *Arch f exper Path u Pharmacol* **120** 16, 1927.

11 Adler, A., and Lemmel, H. *Deutsches Arch f klin Med* **158** 173, 1928.

12 Burger, M., and Habs, H. *Klin Wchnschr* **6** 2221, 1927.

13 Rosenthal, F., Licht, H., and Melchior, E. *Arch f exper Path u Pharmacol* **115** 138, 1926.

14 Stern, R., and Suchantke, G. *Arch f exper Path u Pharmacol* **115** 221, 1926.

15 Mann, F. C. *Modified Physiologic Processes Following Total Removal of the Liver*, *J. A. M. A.* **85** 1472 (Nov. 7) 1925.

16 Bloor, W. R. *J. Biol. Chem.* **24** 227, 1916. Bloor, W. R., and Knudson, A. *J. Biol. Chem.* **27** 107, 1916.

GROUP 1 ACUTE PARENCHYMATOUS DISEASES OF THE LIVER

CASE 1—A man, aged 32, with an unimportant past history, complained of loss of appetite, dark urine, diarrhea, clay-colored stools of ten days' duration and jaundice of six days' duration prior to admission. There was no history of pain, vomiting, fever, chills or previous attacks of jaundice. No medicines had been taken by the patient previously. Physical examination showed deeply jaundiced sclerae and a palpable liver two fingerbreadths below the costal margin, which was not tender. No fluid was present in the abdominal cavity. The spleen was barely palpable. The course of the disease was afebrile throughout. The

TABLE 1—*Determination of Total, Free and Cholesterol Ester Content in the Blood Plasma and Relation to Other Tests in Case 1*

Date	Cholesterol			Urine		Liver Function Test		Van den Bergh		Ester, per Cent
	Total	Ester	Free	Urobilin	Bile	Dye Retention, 30 Min	Icterus Index	Direct	Indirect	
4/ 8*	150	Trace	150	+++	+	60%	70			0
4/10	140	Trace	140		+					0
4/14	102	57	105					Positive	1 11,000	35
4/18*	214	56	158				120			26
4/29	300	120	180				75			40
5/14	312	188	124				20	Delayed positive	1 330,000	60

* Urobilin present in stool

TABLE 2—*Determinations in Case 2*

Date	Cholesterol			Urine		Liver Function Test		Van den Bergh		Ester, per Cent
	Total	Ester	Free	Urobilin	Bile	Dye Retention, 30 Min	Icterus Index	Direct	Indirect	
2/13	260	0	260	+	+	35%	30	Negative	1 500,000	0
2/24	270	0	270	+	+		25	Negative	1 380,000	0
3/ 6	170	114	56	0	0					67
3/11						5%	18			

diagnosis was toxic or infectious hepatitis. The patient improved on a diet high in carbohydrates.

CASE 2—A boy, aged 13, entered another hospital in October, 1929, with a history of lumbar pain, marked icterus and attacks of irregular fever. At that time he was found to have a very large liver and a moderately enlarged spleen. The blood count was normal, and a chemical analysis of the blood gave normal results. Evidences of mild hepatic insufficiency were noted, the icterus index was 20, and urobilinuria was present. On admission to this hospital, in February, 1930, a moderately enlarged, tender liver and a large hard spleen were observed, the patient was slightly icteric and practically afebrile. The condition of the patient improved on a diet high in carbohydrates. Dr. G. Baehr considered this case one of obscure liver disease, probably the result of diffuse hepatitis with disturbance in the function of the liver.

CASE 3—(This patient was seen privately in consultation by Dr. E. Libman, through whose courtesy the chemical studies were made.) A girl, aged 18, single

gave a history of gastro-intestinal upset, with the onset of vomiting which later became bloody and coffee-ground in nature, deepening jaundice, pruritus, very dark urine, light, almost clay-colored stools, slight fever, apathy and drowsiness. Percussion showed that the liver was small. The case was considered by Dr Libman to be one of acute yellow atrophy. The patient died a few days later. Urinalysis showed marked urobilinuria and bilirubinuria, and by the use of the tyrosinase method of Lichtman and Sobotka¹⁷ tryosine was found to be present. The total cholesterol in the blood plasma was 90 mg per hundred cubic centimeters, and the ester fraction of the cholesterol was 0, three days before death.

CASE 4—In a married woman, aged 34, there was a history of progressive enlargement of the abdomen. The condition was first considered to be pregnancy, then it was found to be an enlarged liver. On admission, physical examination

TABLE 3—*Determinations in a Case of Diffuse Hepatitis (Case 4)*

Date	Cholesterol			Urine		Liver Function Test		Ester, per Cent
	Total	Ester	Free	Uro bilin	Bile	Dye Retention, 30 Min	Icterus Index	
2/10	210	57	153	+	0			27
2/20					0	10%	13	
3/ 8	94	Trace	94					Trace

TABLE 4—*Determinations in a Case of Secondary Congestive Atrophy (Case 5)*

Date	Cholesterol			Urine		Stool		Liver Function Test		Van den Bergh		Ester, per Cent
	Total	Ester	Free	Uro bilin	Bile	Uro bilin	Bile	Dye Retention, 30 Min	Icterus Index	Direct	Indirect	
2/13	135	Trace	135	++	0	+	+			Negative	1 300,000	0
2/26	144	44	100	+	0			50%	60			31
2/29	118	0	118	0	0					Positive	1 26,000	0

showed a well developed and nourished woman, with icteric sclerae and an enlarged liver, which occupied the entire abdomen down to the pubis, and was firm, not tender and smooth. Pneumoperitoneum showed a slightly enlarged spleen. A blood count and chemical analysis of the blood gave normal results. Microscopically, a biopsy of the liver showed a diffuse chronic and acute hepatitis. The patient left the hospital shortly afterward.

CASE 5—A man, aged 37, single, had been injured five months before admission in an automobile accident, causing swelling of the right leg. Three months after the injury the abdominal girth became noticeably increased. On admission to the hospital, this condition was found to be ascites, requiring evacuation. Following paracentesis, the liver was palpable and was found to be considerably enlarged. In view of the swelling of the right lower extremity, due to thrombosis of the saphenous vein, the possibility of thrombosis of the hepatic vein was considered. There was moderate polycythemia. The patient became drowsy and

17 Lichtman, S, and Sobotka, H. *J Biol Chem* 85 261, 1929

stuporous, definitely jaundiced and slightly feverish. The liver function was greatly impaired. Thrombosis in the left cerebral hemisphere developed and the patient died in three weeks. Autopsy showed thrombosis of the right saphenous vein and of the branches of the hepatic veins. This thrombosis caused secondary congestive atrophy of the liver.

CASE 6—A man, aged 26, single, showed a typical picture of lobal pneumonia of five days' duration, involving the right and left lower lobes. On admission the patient was in a severely toxic condition with high temperature, and required the continuous administration of oxygen. The disease reached a crisis after three days, and normal temperature was noted thirty-six hours later. While under observation the patient became jaundiced, the liver became enlarged and grew

TABLE 5—*Determinations in a Case of Acute Hepatitis (Case 6)*

Date	Cholesterol			Urine		Ester, per Cent
	Total	Ester	Free	Urobilin	Bile	
4/ 4				++	0	
4/ 6	200	67	133	+	0	31
4/ 9				Trace	0	
4/11	202	156	46	0	0	77

TABLE 6—*Cholesterol Determinations in a Case of Arsenical Toxic Hepatitis (Case 7)*

Date	Cholesterol			Urine		Liver Function Test		Van den Bergh		Ester, per Cent
	Total	Ester	Free	Uro bilin	Bile	Dye Re tention, 30 Min	Icterus Index	Direct	Indirect	
								Prompt positive	Indirect	
2/13*	120	38	82	+	++	100%	120	Prompt positive	1 18,000	52
2/24	290	125	165	+	0		40	Delayed positive	1 330,000	41
2/27	282	118	164	0	0					42
3/ 6	214	106	108	0	0					50
3/13	268	138	130							52

* Bile present in stool

tender, and the urine contained large amounts of urobilin. The condition was evidently acute hepatitis. Following the crisis, the jaundice receded. The patient was discharged as well.

CASE 7—A man, aged 20, single, had had syphilis two years previously. He was treated with arsphenamine, the last injection having been given nine months prior to his admission to the hospital. He had undergone three extensive tattooing operations, the last one had been performed two weeks preceding admission. After this operation there was a mild febrile reaction with loss of appetite and weakness. The patient went to bed, and ate practically nothing. Four days before admission, the urine became very dark. On admission the patient was moderately jaundiced, with an enlarged, tender liver, the spleen was non-palpable. The disease followed an afebrile course. The Wassermann reaction was negative. There were evidences of marked damage of the liver. Arsenic was found in the urine nine months after the last injection of arsphenamine. The case

was considered one of arsenical toxic hepatitis precipitated by recent malnutrition. The patient's condition improved on a diet high in carbohydrate and low in fat.

CASE 8—A man, aged 52, was treated for thrombo-angitis obliterans of four years' duration. He had received intravenous injections of hypertonic saline in doses of from 100 to 150 cc about six times monthly for the past five months (thirty injections). Thirty-six hours after the last injection (seven days before admission to the hospital), malaise and fever with nausea developed. At that time clay-colored stools and dark urine were noted. Two days later definite jaundice and pains in the right lower quadrant of the abdomen were observed. On admission, the patient was deeply jaundiced, the liver was below the costal

TABLE 7—*Determinations in Case 8*

Date	Cholesterol			Urine		Stool		Liver Function Test		Van den Bergh		Ester, per Cent
	Total	Ester	Free	Uro bilin	Bile	Uro bilin	Bile	Dye Retention, 30 Min	Icterus Index	Direct	Indirect	
12/16	238	57	181	+	++	+++		70%	35		1 19,000	24
12/31	250	70	180	++	+	++	+++	35%	30		1 40,000	28
2/10	220	170	50	0	0					Negative	1 500,000	77

TABLE 8—*Values for Cholesterol in a Case of Toxic Hepatitis (Case 9)*

Date	Cholesterol			Urine		Stool		Liver Function Test		Van den Bergh		Ester, per Cent
	Total	Ester	Free	Uro bilin	Bile	Uro bilin	Bile	Dye Retention, 30 Min	Icterus Index	Direct	Indirect	
4/ 2	122	0	122	+	+	++	++					0
4/ 4				++	++			50%	75	Prompt positive	1 30,000	
4/ 8	150	34	116	++			±					23
4/14	276	134	142	++			+		25	Negative	1 330,000	49
4/22								5%	15			

margin and was not tender, and the spleen could not be felt. The case was considered one of acute hepatitis resulting from intravenous infusions of hypertonic saline. The patient was given a diet high in carbohydrates and low in fats, with insulin, and he gradually improved. He was discharged as well at the end of twelve weeks.

CASE 9—A man, aged 40, married, entered the hospital because of loss of weight and generalized adenopathy. Because of restlessness and nervousness, he was given 18 grains (1.16 Gm) of phenobarbital in thirteen days, a diffuse, irregular, macular eruption developed with a temperature that ranged as high as 104 F. The condition was diagnosed as erythema medicamentosum. There was a persistent fever. Then an icteric tint to the sclerae and skin developed with bile and urobilin in the urine. The patient began to vomit, jaundice increased, with diminution in the size of the liver. There was no history of the administration of arsenic. The condition gave the impression of being toxic hepatitis or acute yellow atrophy. With the continuous intravenous injection of dextrose and a diet high in carbohydrates the patient improved gradually.

CASE 10—A woman, aged 31, married, suffered from attacks of painful joints, rash, conjunctivitis and puffiness of the lower lids, lasting from three to five weeks and recurring every three weeks. In February, 1930, the patient was given cinchophen tablets, 5 grains (0.324 Gm), three times daily for three weeks. Then medication was stopped for six weeks. In April, she was given 5 grain cinchophen tablets three times daily for five days. After ten tablets had been administered, generalized pruritus developed with dark-colored urine, containing bile. Ten days after the administration of the last tablet, icteric sclerae and skin and whitish stools were noted. For from four to five days before admission, there was a fever ranging from 100 to 104 F with chilly sensations. Physical examination showed marked jaundice, and at a hand's breadth below the costal margin the liver was firm, smooth and not tender. The spleen was palpable. The condition was considered one of toxic hepatitis or of early yellow atrophy following medication with cinchophen. The patient was put on a diet high in carbohydrates, and improved.

TABLE 9—*Determinations in a Case of Toxic Hepatitis (Case 10)*

Date	Cholesterol			Urine		Stool		Liver Function Test		Van den Bergh		Ester, per Cent
	Total	Ester	Free	Uro bilin	Bile	Uro bilin	Bile	Dye Retention, 30 Min	Icterus Index	Direct	Indirect	
5/ 7				+	+	+	+	60%	100	Prompt positive	1 12,000	
5/10	140	0	140	+	+							0
5/16				+	+				100	Delayed positive	1 50,000	
5/17	154	64	90									42
5/26	312	170	142			+	+		100	Positive	1 50,000	51
5/28				++	0			50%	67			
6/ 2	208	125	83									60

A perusal of the aforementioned results shows several interesting observations. In case 1, in which the condition was evidently catarrhal icterus or toxic hepatitis, the total cholesterol of the blood was normal, whereas the cholesterol ester was practically nothing at the onset of the disease at the time when the liver function was markedly diminished, as evidenced by the urobilinuria, the considerable retention of the injected dye and the high icteric index. On a diet high in carbohydrates, there was a gradual improvement in the condition, and with this a gradual rise in the absolute and relative values for ester, until, before discharge, the percentage of the ester was normal. The second case was one of diffuse hepatitis of obscure origin, with urobilinuria and retention of dye. The cholesterol ester was entirely lacking in the beginning, but with improvement in the general condition of the patient, the ester portion rose to 67 per cent of the total cholesterol, which is the normal ratio of ester to total cholesterol. Case 3 was clinically considered as one of acute yellow atrophy, with the presence of tyrosine in the urine. The blood plasma showed a low total cholesterol of only 94, and the ester portion was entirely missing. Case 4 presented a puzzling problem.

The only observations were urobilinuria and a tremendously enlarged, smooth liver, the icterus index and the dye retention test of the liver were normal. However, the values for cholesterol ester were relatively and absolutely low at first and then disappeared. There seemed to be some discrepancy here since the test for liver function showed a normally functioning liver, whereas the ester disappearance pointed to considerable damage. However, a laparotomy was performed and the biopsy of the liver showed a diffuse chronic and acute hepatitis, thereby confirming the impression of liver damage as evidenced by the low ester values. In case 5, with the interesting condition of thrombosis of the hepatic veins and the subsequent congestive atrophy of the liver, there was noted at first a trace of ester, but shortly thereafter a total disappearance of the cholesterol ester followed by the death of the patient in a few days. In case 6, a typical lobar pneumonia, with some damage of the liver, developed, as shown by the urobilinuria and jaundice. The total cholesterol in the blood plasma was within normal limits, and the cholesterol ester was depressed, but not markedly. This seemed to point to a mild hepatitis, especially as the ester returned to normal in five days and the patient became well. Cases 7, 8, 9 and 10 are all instances of acute hepatitis following medication. In each case there were ample evidences of severe damage of the liver, such as jaundice, urobilinuria, a high icterus index, or marked retention of the dye in the bromsulphalein test. The figures for cholesterol ester in the blood plasma were either considerably depressed or zero, seemingly dependent on the severity of the damage. With the institution of diets high in carbohydrate, the cholesterol esters rose until they reached normal absolute and relative values, the rise being concomitant with the gradual improvement in the condition of the patients.

Of particular interest is the fact that in cases 1, 6, 7, 8, 9 and 10, concomitantly with the clinical improvement and the regression of the evidences of damage of the liver, the total cholesterol and the ester figures rose beyond those found in normal blood plasma. This significant observation is being further studied. Apart from the theoretical side, it already has a value in demonstrating that unless cases are followed from beginning to end, the figures for the cholesterol and its ester, taken at varying times in the course of a given disease process, might give diverse results to different observers. A single analysis taken at random might yield a distorted picture of the condition, owing to the early restoration of the ester fraction during periods of recovery (see cases 1, 6, 9 and 10).

GROUP 2 ATROPHIC CIRRHOSIS OF THE LIVER

This type of hepatic disease, a process slow and long drawn out in its evolution, and in which there is ample time for regeneration, offers

a contrast to the rapidly progressing acute parenchymatous damage of the liver. Table 10 comprises the chemical determinations in these cases. A brief summary of the clinical history and physical observations is given.

CASE 1—A man, aged 39, single, had been admitted to the hospital three years previously with a history of chronic alcoholism, morning retching, vomiting, increasing weight and loss of strength. Ascites was present. He used alcohol to excess. Three months prior to the second admission to the hospital there were slight painless hematemesis and melena, morning retching and soreness of the epigastrium. The edge of the liver was palpated three fingerbreadths below the costal margin, it was smooth, rounded and not tender. Ascites was not present. The Wasseimann reaction was negative. Four years prior to admission and on admission the case was considered one of alcoholic cirrhosis of the liver.

TABLE 10—*Chemical Determinations in Four Cases of Atrophic Cirrhosis of the Liver*

Case	Cholesterol			Urine		Liver Function Test		Van den Bergh		Ester, per Cent
	Total	Ester	Free	Urobilin	Bile	Dye Retention, 30 Min	Icterus Index	Direct	Indirect	
1	190	100	90							53
	160	105	55	+	0	5%	10	Negative	1 500,000	68
2	203	140	63			0	8			67
3	156	117	39	+	0					75
4	195	91	104	++	Trace			Delayed positive	1 100,000	48
	210	114	96	+	Faint trace	25%	25			51

CASE 2—A widow, aged 61, had a history of repeated alcoholic sprees for the past five years, with epigastric distention, belching and other disturbances. There was no melena or hematemesis. Before admission, incessant vomiting and jaundice developed, following repeated sprees. The patient entered the hospital with a subicteric tint to the sclerae and skin, and an enlarged, hard and irregular liver. The spleen was not palpable. A roentgenogram of the gastro-intestinal tract was negative. The impression gained was that the condition was cirrhosis of the liver.

CASE 3—A man, aged 64, single, had a history of unlimited indulgence in liquor for many years. Six weeks before admission, swelling of the lower extremities was noted, three weeks later rapid swelling of the abdomen, poor appetite and abdominal cramps were observed. On admission the following observations were made: slight icterus, enormous ascites, enlarged superficial veins, scleroderma of the lower extremities, absence of axillary and pubic hair, diminutive genitalia and peculiar thin skin, suggestive of the constitutional type seen in cirrhosis. After paracentesis of 10 liters (1 Kg) of clear fluid, a coarsely irregular edge of the liver and the spleen were felt. The fluid rapidly reaccumulated, followed by death. Autopsy showed atrophic portal cirrhosis with adenoma.

CASE 4—In a widow, aged 40, jaundice developed following an alcoholic spree six weeks before admission. The condition was painless, and it was accompanied

by light-colored stools. On admission, the liver was found to be enlarged four fingerbreadths below the costal margin. The spleen was palpable, and there was moderate jaundice. The gastro-intestinal series was negative. The case was considered typical of cirrhosis of the liver.

In this group of cases of atrophic cirrhosis, it will be seen that the cholesterol in the blood plasma lies within normal limits for the total values as well as for the ester portion. This preservation of the ability of the liver to esterify the free cholesterol agrees with the general observations that in uncomplicated cases of cirrhosis of the liver—in noncholemic stages—the functions of the liver are very little impaired. This is in agreement with the observations of Adler and Lemmel, who also found normal or only slightly lowered values for cholesterol and for ester in the blood in cases of cirrhosis of the liver, in which the patients were not in the precomatose or comatose condition.

COMMENT

The most striking changes have been encountered in the values for cholesterol ester of the plasma. The figures for cholesterol ester have run more or less parallel to the severity of the damage, as measured by the general condition of the patient and the signs of damage of the liver commonly employed, namely, urobilinuria, jaundice, increased icterus index and abnormal retention of bromsulphalein. When the damage has been most severe, the ester fraction has been markedly depressed or even entirely absent, and when there has been improvement in the cases, the ester values have risen until, relatively and absolutely, the normal proportions have been reached.

To account for this phenomenon the suggestion has been made that, with acute diffuse parenchymatous damage, the liver loses its function to esterify the free cholesterol with the fatty acids, and that this property of the liver is a sensitive one and readily disturbed. It is also conceivable that through such damage of the liver the ester might disappear through an enhanced enzymatic activity resulting in increased splitting of the cholesterol ester. However, it seems more probable that the disappearance of the cholesterol ester is due to the loss of the ability of the liver to esterify the free cholesterol.

In four cases of atrophic cirrhosis of the liver, in which the damage to the liver was not appreciable and in which the process slowly developed with an opportunity for ample regeneration, the functions of the liver were not markedly disturbed. Concomitantly, it will be seen that the values for cholesterol, both total and ester, have been within the normal or slightly subnormal range.

From this series of cases, and from the work of certain authors previously mentioned, it can be seen that the values for cholesterol ester

in the blood plasma seem to parallel other evidences of damage of the liver and that the depression or disappearance of the ester goes hand in hand with the reduced function as estimated by the other tests for liver function. It seems, therefore, that through the simple determinations of the total cholesterol and cholesterol ester, on from 1 to 2 cc of fasting blood plasma, one might find a way to eliminate the tedious and complicated methods of testing the liver function, especially since by this most convenient method, repeated values can be obtained at short intervals throughout the entire process of the disease. It will be found to be not only of diagnostic but also of some prognostic aid.

Studies are now being directed to the cases of calculous disease, with and without complications of hepatic disease and infection, in an attempt to arrive at a convenient means of estimating the amount of damage of the liver caused by the stasis in the biliary passages.

SUMMARY

- 1 An added insight into the complex problem of liver function seems to be gleaned from the determination of the total and cholesterol ester, a simple method that requires only from 1 to 2 cc of blood plasma, and that can be repeated throughout the course of the disease.

- 2 Ten cases of acute diffuse parenchymatous damage of the liver have been studied. The cholesterol ester values in the blood plasma were found to be diminished or entirely absent, corresponding with the severity of the diseased process. With the improvement in the condition the ester values rose to their absolute and relative normal proportions. This progress as revealed by the ester values paralleled in large measure the general condition of the patient and the other liver function tests.

- 3 In four cases of atrophic cirrhosis of the liver, with its slow evolution, slight damage and ample regeneration, the cholesterol partition was normal.

- 4 The ester values seem to offer some means of diagnosing parenchymatous damage of the liver and, when repeated during the course of the disease, some prognostic significance.

POLYCYTHEMIA VERA AND CHRONIC PULMONARY DISEASE *

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Weber ¹ divided cases of polycythemia into three groups (1) relative polycythemia due simply to concentration of the blood, (2) secondary polycythemia due to high altitude, cardiopulmonary disease, blood stasis in other organs or toxemia, such as poisoning by phosphorus and infectious diseases and (3) true erythremia due to primary idiopathic excessive erythroblastic activity in the bone marrow

Polycythemia vera (erythremia, Vaquez' disease or Osler's disease) has been defined as a "morbid condition, characterized by a well marked, persistent relative and absolute polycythemia, due to an excessive erythroblastic activity of the bone marrow which appears to be the primary morbid factor" As to the agent or mechanism responsible for this disturbed function of the bone marrow, there is only speculation Osler suggested that eventually all types of polycythemia would be found to be secondary Even if this proves to be correct, it may be assumed that the polycythemia in some cases constitutes a simple response to increased demand on the blood for oxygen-carrying power and is therefore beneficial, and that in other cases it progresses to the point of causing symptoms and even menacing the patient's life through the extensive changes in the character and volume of the blood Harrop ² advanced the suggestion that if there is an abnormal stimulus which provokes the bone marrow to excessive erythroblastic activity, there may be a tremendous variation in the individual responses, and that if an unbalanced proliferation has once been started, it may become impossible to restore the normal mechanism, in some cases at least, even if the original stimulus is removed

The work on the volume of the blood, particularly that done by the use of dyes—vital red as used by Keith, Rowntree and Geraghty,³ and

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² With the technical assistance of Grace M Roth

1 Weber, P F Polycythaemia Erythrocytosis and Erythraemia (Vaquez-Osler Disease), New York, Paul B Hoeber, Inc 1922, pp 144

2 Harrop, G A, Jr Polycythemia, *Medicine* **7** 291 (Aug) 1928

3 Keith, N M, Rowntree L G, and Geraghty, J T A Method for the Determination of Plasma and Blood Volume *Arch Int Med* **16** 547 (Oct) 1915

congo red as used by Harris,⁴ Griesbach,⁵ and Rowntree and Brown⁶—has introduced a new method of approach in the diagnosis of polycythemia. Brown and Giffin,⁷ and Rowntree and Brown found striking increases in the volume of the blood by this method in cases of polycythemia. Lemon⁸ recently reported studies of the volume of the blood by the same method in twelve cases of chronic bronchitis and emphysema associated with significant grades of cyanosis. Further evidence of anoxemia was indicated by the saturation of oxygen in the arterial blood in seven of these cases, it varied between 83 and 93 per cent, definitely below normal. The lowest values for volume blood in the group of polycythemia were 117 cc for each kilogram of body weight and 4,300 cc for each square meter of body surface, whereas the highest values in the group of chronic pulmonary disease were 103

TABLE 1—Summary of Statistics of Blood Volume Obtained by the Use of Congo Red

Authors	Diagnosis	Cases	Blood Volume, Cc for Each Kg of Body Weight			Blood Volume, Cc for Each Sq M of Body Surface		
			Mean	High	Low	Mean	High	Low
Rowntree and Brown	Normal subjects	74	87.7	107	66	3,278	4,050	2,685
Brown and Giffin	Polycythemia vera	14	166.0	209	117	5,850	7,650	4,300
Rowntree and Brown	Polycythemia vera	50	167.0	216	121	6,056	8,660	4,540
Lemon	Chronic pulmonary disease with cyanosis	12	91.5	108	82	3,367	3,700	2,950

cc for each kilogram of body weight and 3,700 cc for each square meter of body surface, which are within normal limits (table 1). Lemon's twelve cases provided strong evidence that chronic anoxemia of the arterial blood due to pulmonary disease does not produce a significant increase in the volume of the blood. He also mentioned two cases in which the volume was high, in these cases there were splenomegaly, chronic pulmonary disease and cyanosis. He considered that these were cases of polycythemia vera with associated pulmonary disease.

4 Harris, quoted by Rowntree and Brown (footnote 3)

5 Griesbach, W. Ein klinisch brauchbare Methode der Blutmengenbestimmung, *Deutsche med. Wchnschr.* **47** 1289 (Oct. 27) 1921

6 Rowntree, L. G., and Brown, G. E. *The Volume of the Blood and Plasma in Health and Disease*, Philadelphia, W. B. Saunders Company, 1929, p. 209

7 Brown, G. E., and Giffin, H. Z. Studies of the Vascular Changes in Cases of Polycythemia Vera, *Am. J. M. Sc.* **171** 157 (Feb.) 1926

8 Lemon, W. S. A Study of the Effect of Chronic Pulmonary Diseases on the Volume and Composition of the Blood, *Ann. Int. Med.* **3** 430 (Nov.) 1929

It is my object in this paper to report four cases in which there were definite polycythemia and pulmonary disease and to consider them from the standpoints of diagnosis, pathogenesis and results of treatment by destruction of blood

REPORT OF CASES

CASE 1—A Chinese cook, aged 40, from Deadwood, S D, came to the clinic on April 9, 1928, complaining of increasing dyspnea and exhaustion on exertion, of three years' duration, which gradually became so severe that he could walk no more than four blocks without resting. He had been subject to frequent attacks of respiratory infection with short attacks of cough, asthma and dyspnea during most of his life. He had had a swelling of the ankles for one year, and this had increased until it involved the entire lower extremities, the lower portion of the abdomen and the back.

General examination disclosed cyanosis, which was detectable in spite of the patient's naturally dark skin, generalized edema of moderate degree and a slight enlargement of the liver and the spleen. There was enlargement of the heart to the right and left with distant heart tones and a soft systolic murmur at the apex. There were scattered moist râles at the base of both lungs. The blood pressure was 110 systolic and 70 diastolic in millimeters of mercury. The first Wassermann test of the blood gave a weak positive reaction but five subsequent tests gave negative reactions, one Wassermann test of the spinal fluid was negative. Analysis of the blood showed the concentration of the hemoglobin at 19 Gm per hundred cubic centimeters, 5,290,000 erythrocytes and 4,200 leukocytes in each cubic millimeter of blood. Fluoroscopic and stereoscopic roentgenographic examinations of the thorax gave negative results. The electrocardiogram showed evidence of right ventricular preponderance, and there were inverted T waves in all three derivations. The hematocrit reading showed 70 per cent cell and 174 cc of blood for each kilogram of body weight. At this time the patient was treated with digitalis and theophylline-ethylene diamine, and he gradually improved in a month. He became free from edema, was much less dyspneic and was able to walk a mile without shortness of breath. The cyanosis, however, persisted.

The patient returned to the clinic on October 1, after changing his residence to Salida, Colo (altitude 7,000 feet [2,000 meters]). He stated that the dyspnea had returned six weeks previously, followed by a cough and edema as before. Examination revealed marked cyanosis, marked dyspnea and dilated conjunctival veins. The heart was definitely enlarged, especially to the right. There was a systolic murmur at the apex and in the pulmonic area. The heart tones were somewhat muffled. The thorax was emphysematous with poor expansion. Harsh breath sounds were heard over the upper part of the thorax, and many coarse râles were heard over the base of both of the lungs. The edge of the liver was 3 cm below the right costal margin, and the spleen was not palpable. There was slight but definite edema of the lower part of the legs. The blood pressure was 100 systolic and 60 diastolic. The Wassermann reaction of the blood was again negative. The electrocardiogram gave evidence of a right ventricular preponderance, and there were inverted T-waves in derivations II and III.

The patient was treated with ammonium nitrate and theophylline-ethylene diamine, and was given 0.5 cc of salyrgan intravenously, after which there was marked diuresis and disappearance of the edema. The respiratory symptoms and cyanosis persisted. He was then given 0.1 Gm of phenylhydrazine three times a day until a total of 2.8 Gm had been given. The decrease in the number of erythrocytes and the volume of blood and the relief from respiratory symptoms were striking, as shown in table 2.

Comment—The pathogenesis in this case is not entirely clear. The history was one of chronic recurrent respiratory disease culminating in cardiac decompensation. The observations were those of failure of the right side of the heart and advanced pulmonary disease with marked cyanosis and polycythemia out of all proportion to what one might expect as a compensatory phenomenon. This clinical picture was similar to that described as Ayerza's disease. There is much disagreement in the literature regarding the exact definition of this condition. Arrillaga⁹ expressed the belief that syphilitic arteritis with occlusion of the pulmonary arterioles is the essential lesion, but that chronic bronchitis might precede this process for a number of years. Cheney¹⁰ expressed the belief that primary chronic bronchitis followed by superimposed syphilitic pulmonary arteritis produced the clinical picture. Recently,

TABLE 2—Data in Case 1

Time of Observations	Hemoglobin (Acid Hematin), Gm for Each 100 Cc of Blood	Erythrocytes, Millions	Cells by Hematocrit, per Cent	Blood Volume, Cc for Each kg. of Body Weight	Blood Volume, Cc for Each Sq. M. of Body Surface	Vital Capacity, Cc	Symptoms, Grade
Before treatment with phenylhydrazine	25.3	7.67	72	185	6,160	1,075	Cough, 2 Dyspnea, 3 Cyanosis, 3
Two weeks after course of phenylhydrazine was completed	12.0	4.16	32	106	3,195	2,230	Cough, 1 Cyanosis, 1

the influence of syphilis has been questioned, and cases have been reported in which there was no evidence of syphilis. Moschcowitz¹¹ considered such a clinical syndrome as best called hypertension of the pulmonary circulation and expressed the belief that the bronchitis is usually primary and the vascular disease secondary to this hypertension. It is difficult, if not impossible, to make a definite diagnosis of Ayerza's disease during life. Polycythemia in these cases, as evidenced by a high erythrocyte count, is considered a cardinal symptom, but data concerning blood volume in proved cases of Ayerza's disease are lacking. In case 1, there is evidence of hypertension of the pulmonary circulation.

9 Arrillaga, F. C. *La Arteritis Pulmonar y su Cuadro Clínico*, Buenos Aires, 1925.

10 Cheney, Garnett. Ayerza's Disease, *Am J M Sc* **174** 34 (July) 1927.

11 Moschcowitz, Eli. Hypertension of the Pulmonary Circulation, Its Causes, Dynamics, and Relation to Other Circulatory States, *Am J M Sc* **174** 388 (Sept.) 1927.

but it is not possible to rule in or out the presence of organic pathologic changes in the pulmonary arteries, hence I hesitate to use the term Ayerza's disease. In any event, the polycythemia was extreme as evidenced by the blood volume, hematocrit readings and viscosity, it was felt that this constituted a menace to an already weakened heart and embarrassed pulmonary circulation. It would seem that this conception was justified by the response to treatment by phenylhydrazine. I believe that the case should be considered one of polycythemia vera because of the high blood volume, although the question of chronic pulmonary disease with anoxemia as the original stimulus to the bone marrow cannot be excluded.

TABLE 3—Data in Case 2

Time of Observations	Hemoglobin (Acid Hematin), Gm for Each 100 Cc of Blood	Erythrocytes, Millions	Cells by Hematocrit, per Cent	Blood Volume, Cc for Each Kg. of Body Weight	Blood Volume, Cc for Each Sq. M. of Body Surface	Blood Viscosity	Vital Capacity, Cc	Symptoms, Grade
Before treatment with phenylhydrazine	25.0	5.97	75	168	6,020	13.4	1,996	Dyspnea, 3 Asthma, 3 Cyanosis, 3 Headache, 2
Five days after second course of phenylhydrazine was completed	19.2	4.91	59	152	5,300	7.4	3,780	None

CASE 2—A Swedish laborer, a resident of Denver (altitude 5,200 feet [1,500 meters]), came to the Mayo Clinic on June 24, 1929, complaining of dyspnea and asthma. He had noticed blueness of the hands and the face for seven years, and during that time he had had occasional attacks of dyspnea and tightness in the thorax. Three years previously he had pneumonia followed by recurrent asthmatic and dyspneic attacks with a productive cough. These had gradually increased in frequency and severity. Ten months prior to his visit to the clinic he consulted a physician because of headaches and redness and soreness of the eyes. Hematuria was found at that time. Venesection was done several times, which resulted in weakness but temporary relief from the thoracic symptoms. He lost 25 pounds (11.3 Kg.) in weight in ten months and had not worked during that time.

General examination disclosed marked cyanosis of the entire body, particularly of the face and the hands, with deep purplish-red lips and oral mucosa. The conjunctival veins were engorged. The large superficial veins all over the body were prominent. The patient was very dyspneic even while at rest with wheezing asthmatic respiration. The thorax was emphysematous with poor expansion and hyperresonance. Expiratory musical râles were heard throughout the lungs. The heart was slightly enlarged, and the radial arteries were definitely sclerosed on palpation. The spleen was not palpable. The blood pressure was 120 systolic and

85 diastolic. The urine contained albumin, grade 2, and erythrocytes, grade 3. Roentgenographic examination of the kidneys gave negative results. Roentgenographic examination of the thorax gave evidence of marked fibrosis of both lungs with localized bronchiectasis of the left lower lobe. The electrocardiogram indicated the presence of a right ventricular preponderance and a slightly delayed conduction time.

The patient was given two courses of phenylhydrazine hydrochloride, 0.1 Gm three times a day, with a period of rest of two weeks between courses. The first course totaled 1 Gm and the second 1.6 Gm. Although the reduction in blood was not striking, the symptomatic relief was definite. Rest may have played some part in the latter, since the patient was kept in bed during the first course of phenylhydrazine. The results are given in table 3.

TABLE 4—Data in Case 3

Time of Observations	Hemoglobin (Acid Hematin), Gm for Each 100 Cc of Blood	Erythrocytes, Millions	Cells by Hematocrit, per Cent	Blood Volume, Cc for Each Kg. of Body Weight	Blood Volume, Cc for Each Sq. M. of Body Surface	Blood Viscosity	Oxygen Saturation of Arterial Blood, per Cent	Vital Capacity, Cc	Symptoms, Grade
Before treatment	25.0	5.60	66	140	4,875	12.2	87	3,806	Dyspnea on exertion, 1 Cyanosis, 2 Edema of legs, 2
Nine days after course of phenylhydrazine was completed	10.2	4.73	32	96	3,450	4.4		4,150	Edema of legs, slight, ulcer almost healed

Comment—If the history is reliable in this case, polycythemia preceded the bronchitis and asthma. I consider this case one of polycythemia vera in which the pulmonary condition was either an unrelated complication or secondary to stasis of the pulmonary circulation. Therefore the patient was treated by destruction of blood, cautiously at first because of asthma and cardiac embarrassment.

CASE 3—A coal miner, aged 49, of Superior, Wyo. (altitude 6,500 feet [1,900 meters]), came to the Mayo Clinic on Nov. 26, 1929, complaining of swelling of the legs, varicose veins and an ulcer of the lower part of the right leg. His father had died of "miner's asthma." The patient's color had been dusky for at least eleven years, it had been much worse during frequent respiratory infections, in 1918, 1927 and 1928 he had had pneumonia, during which he had been "as black as a Negro." He had moderate dyspnea on exertion since the first attack of pneumonia. He had known of the varicose veins in both of the legs for at least ten years, and there had been pigmentation of the lower part of the legs for at least six years. After the pneumonia in 1928, he had phlebitis of both legs, with considerable pain and edema, and since that time his legs had become considerably swollen at the end of the day. A spontaneous ulcer developed above the right internal malleolus in the month prior to admission.

The color of the face and body was ruddy and cyanotic, and there was purplish cyanosis, grade 3, of the lips. The conjunctival veins were dilated and all the larger superficial veins of the body were prominent. There were varicose veins, grade 3, of the right leg and grade 2 of the left leg with much pigmentation over the lower part of both of the legs. There was edema, grade 2, just above both of the ankles and a clean, granulating ulcer, 2 cm in diameter, just above the right internal malleolus. Examination of the heart, the lungs and the abdomen gave negative information. The spleen was not palpable. Roentgenographic examination of the thorax gave evidence of diffuse fibrosis of the lower half of both of the lungs, apparently pneumoconiosis. The electrocardiogram indicated the presence of right ventricular preponderance, but otherwise the evidence was negative. The patient was given 27 Gm of phenylhydrazine over a period of nine days. A marked decrease in the erythrocyte count and in the blood volume resulted with improvement in the condition of the leg and disappearance of the cyanosis, as shown in table 4.

TABLE 5—Data in Case 4

Time of Observations	Hemoglobin (Acid Hematin), Gm for Each 100 Cc of Blood	Erythrocytes, Millions	Cells by Hematocrit, per Cent	Blood Volume, Cc for Each Kg of Body Weight	Blood Volume, Cc for Each Sq M of Body Surface	Blood Viscosity	Oxygen Saturation of Arterial Blood, per Cent	Vital Capacity, Cc	Symptoms, Grade
Before treatment	23.6	6.52	65	105	4,655	9.6	83.7	3,000	Cough, 2 Dyspnea, 1 Asthma, 2 Headache, 2 Pain in thorax, 2
One week after course of phenylhydrazine was completed	19.5	4.55	58	88	3,700	7.2		4,000	Cough, 1

Comment—The question as to whether the polycythemia or the respiratory disease was the first episode in this case cannot be answered. It would seem that cyanosis was first definitely noticed at the time of the first attack of pneumonia. In any event, the polycythemia was out of all proportion to what one might expect from the pulmonary disease. The question was raised as to whether this patient's blood should be reduced at all, since he had so few symptoms, but the high blood volume as an added factor in producing increased venous pressure and edema in the legs seemed to justify this method of treatment.

CASE 4—A Russian farmer from Kamsack, Saskatchewan (altitude 2,000 feet [600 meters]), aged 43, registered at the Mayo Clinic on Dec 23, 1929, with the complaint of dyspnea and headaches. His face had been dusky red for at least three years, and he had had a chronic cough for three years with paroxysms at night. For one year there had been increasing dyspnea on exertion and attacks of nocturnal dyspnea and orthopnea with the coughing spells. Occasionally he had attacks of substernal pain radiating into both sides of the thorax after

exertion, and these were relieved by rest. For six months he had had pain in various parts of the head, especially after exertion and in hot weather.

The patient was large and obese with ruddy cyanosis of the face and the hands. There was marked telangiectasis of the cheeks. The veins of the conjunctiva were dilated and the lips and oral mucosa were a deep, bluish red. The thorax was thick in the anteroposterior diameter, with poor expansion, hyperresonance, distant breath sounds, prolonged expiration and many dry musical and coarse moist râles. Examination of the heart gave negative information. The abdomen was obese, and the spleen was barely palpable. There was sclerosis, grade 1, of the radial arteries. The veins of the ocular fundi were dilated. A roentgenogram gave evidence of considerable fibrosis of both lungs.

The patient was given 21 Gm of phenylhydrazine over a period of one week. Symptomatic improvement was observed after the first three days of the treatment and was continued during the entire period of observation. The results are given in table 5.

Comment—In this case, with blood volume of only 105 cc for each kilogram of body weight, the diagnosis of polycythemia vera may be questioned since this figure is within the normal limits and only 2 cc higher than the highest figure in Lemon's series (table 1). However, the patient was definitely obese, and therefore the volume for each square meter of body surface is much more accurate for comparative purposes, as shown by Rowntree and Brown in their table of normal blood volume. The blood volume for each square meter of body surface, in this case, was 4,655 cc and would fall definitely into the group of polycythemia vera. The response to treatment by phenylhydrazine was good from both the symptomatic and objective standpoints.

COMMENT

Cases in which both polycythemia and chronic pulmonary disease are present may be considered in four groups in regard to the relative pathogenesis. In group 1 are cases of primary pulmonary disease with compensatory polycythemia. Such a condition apparently was present in a number of Lemon's cases in which the concentration of hemoglobin, the number of erythrocytes and the percentage of cells as determined by the hematocrit were all high. However, the blood volume in these cases was within normal limits, and until additional data are presented, I shall believe that high blood volume is not produced as a compensatory phenomenon and, if present, represents either overcompensation or an independent condition.

In group 2 are cases of primary pulmonary disease initiating polycythemia which progresses beyond the point of a compensatory response to produce symptoms and to become a menace in itself. In such cases the blood volume may be high. As Harrop has said, only certain persons might be capable of such a response of the bone marrow.

In group 3 are cases of polycythemia vera with complicating but unassociated pulmonary disease. Here it might be assumed that the condition in the lung had no influence on the blood, or again, that it might be enough of an added factor to convert an already existent mild polycythemia vera into a severe polycythemia vera.

In group 4 are cases of polycythemia vera causing or predisposing to pulmonary disease. Harrop stated that dyspnea on exertion is frequently observed in polycythemia vera even in the absence of cardiac or pulmonary disease, that reduced vital capacity and pulmonary congestion are not uncommon and that many of these patients acquire respiratory infection easily. It is also possible that a vicious circle might be set up, each of the conditions tending to aggravate the other.

In a case in which chronic pulmonary disease and elevation of the hemoglobin and erythrocyte count are present, the most important consideration would seem to be whether the polycythemia was compensatory, and therefore beneficial and to be left alone, or whether it was excessive, productive of symptoms or of danger to the patient and therefore to be treated. The height of the blood volume appears to be a definite way of determining into which group the case falls, thereby separating the cases in group 1 from those in groups 2, 3 and 4.

There were certain noteworthy features in the four cases presented. An enlarged spleen was not an outstanding observation. In case 1, there was slight but definite enlargement. In cases 2 and 3, the spleen was not felt. In case 4, enlargement was questionable. In most cases of uncomplicated polycythemia vera the spleen is definitely enlarged. The influence of the occupation of the patient on the pulmonary disease is worthy of consideration since two of the men had been miners and the third had worked as a cook in a mining camp. Furthermore, there is the question of the influence of altitude. The patients in the first three cases lived at definitely high altitudes, and the patient in the fourth case lived at a moderately high altitude.

The method used for destruction of the blood, namely, the administration of phenylhydrazine hydrochloride, was first described by Eppinger and Kloss,¹² in 1918, in Germany, and by Owen¹³ in 1924, in the United States. Brown and Giffin,¹⁴ in 1926, reported successful

¹² Eppinger, H., and Kloss, K. Zur Therapie der Polysythämie, *Therap Monatschr* **32** 322, 1918.

¹³ Owen, Trevor. A Case of Polycythaemia Vera with Special Reference to the Familial Features and Treatment with Phenylhydrazine, *Bull Johns Hopkins Hosp* **35** 258 (Aug.) 1924.

¹⁴ Brown, G. E., and Giffin, H. Z. The Treatment of Polycythemia Vera (Erythremia) with Phenylhydrazine. *Arch Int Med* **38** 321 (Sept.) 1926.

treatment with phenylhydrazine in seven cases of polycythemia vera Giffin,¹⁵ in commenting on the treatment of polycythemia vera, considered it the most satisfactory form of treatment for patients aged less than 60 years in whom the condition is not far advanced and who can be treated as ambulatory patients. It is recognized that the drug is potent and that it should be used with caution. Accidents during its administration have been described by Giffin and Conner.¹⁶ In the cases reported here, untoward results were not seen.

The relief of respiratory symptoms, as well as those solely due to the polycythemia, was definite in all the cases and would tend to show that pulmonary congestion from the polycythemia was a definite added load to the chronic pulmonary disease.

SUMMARY

Four cases of polycythemia and chronic pulmonary disease with blood volume comparable to that seen in polycythemia vera are reported. Treatment in these cases was by the administration of phenylhydrazine hydrochloride, there was a definite reduction in the blood volume with clinical subjective and objective improvement. Because of the high blood volume and a good response to treatment by destruction of blood these cases are best considered as polycythemia vera with associated or complicating pulmonary disease.

15 Giffin, H. Z. The Treatment of Polycythemia Vera (Erythremia) in Billings and Forsheimer's System of Therapeutics (suppl.), New York, D. Appleton & Company, 1929, p. 461.

16 Giffin, H. Z. and Conner, H. M. The Untoward Effects of Treatment by Phenylhydrazine Hydrochloride. J. A. M. A. **92**: 1505 (May 4) 1929.

CHEMISTRY AND METABOLISM IN EXPERIMENTAL YELLOW FEVER IN MACACUS RHESUS MONKEYS

III BLOOD SUGAR AND LIVER GLYCOGEN *

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AND

CLARE A MORRELL, A M

NEW HAVEN, CONN

It is apparent from the results reported in previous papers of this series,¹ that the hepatic functions of urea formation and deamination are considerably deranged in the terminal stages of yellow fever. These derangements are not apparent earlier in the course of the disease and do not occur in animals that eventually recover.

The liver also plays an important part in carbohydrate metabolism, serving as a reservoir for glycogen and regulating the concentration of blood sugar. Its significance in this respect is evidenced in the inability of dehepatized animals to maintain blood sugar at normal levels, with the consequent development of hypoglycemic shock. Other experimental procedures, such as the exclusion of the blood supply to the liver or the administration of hepatic poisons, have almost invariably resulted in terminal hypoglycemia. Since the liver suffers extensively from the yellow fever virus, one would expect changes in the blood sugar and glycogen content of the liver as a result of the hepatic lesions. The experiments reported in the following pages were performed to find out whether such was the case.

METHODS

Methods of taking blood samples and handling monkeys have been described in a previous report.² The blood sugar determinations were made either by Benedict's method,³ or, in the case of simultaneous arterial and venous blood sugars, by a micromodification described by Friedenson and others.⁴

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* The studies and observations on which this paper is based were conducted with the support and under the auspices of the International Health Division of the Rockefeller Foundation.

1 Wakeman, A. M., and Morrell, C. A. Chemistry and Metabolism in Experimental Yellow Fever in Macacus Rhesus Monkeys. I. Concentration of Nonprotein Nitrogenous Constituents in the Blood, *Arch Int Med* **46** 290 (Aug) 1930, II Nitrogen Metabolism, *ibid* **46** 382 (Sept) 1930.

2 Wakeman and Morrell (footnote 1, first reference).

3 Benedict, S. R. *J Biol Chem* **68** 759, 1926.

4 Friedenson, M., Rosenbaum, M. K., Thalheimer, E. J., and Peters, J. P. *J Biol Chem* **80** 269, 1928.

To obtain simultaneous arterial and venous blood samples, the following technic was resorted to. Animals were either anesthetized with iso-amylethylbarbiturate given intraperitoneally, or by an injection of para-aminobenzoyl-ethylphthalamate at the site of the proposed incision over the femoral vessels. An incision about 2 inches (5 cm) long was then made in the skin, and the femoral artery and vein were exposed. Small gage needles attached to 2 cc syringes were then inserted into the vessels simultaneously, pointing in the opposite direction to the blood current. In the case of arterial blood, the pressure from the vessel itself was usually sufficient to push out the plunger. About 0.5 cc of blood was collected from the artery and vein and transferred immediately to clean, dry, small-bore test tubes of about 5 cc capacity, 0.2 cc of this blood was at once transferred into the measured sulphuric acid, and the sugar determination was carried out in the regular manner.

Slight pressure on a gauze pad applied over the incision before removal of the needles prevented any appreciable loss of blood until the punctures in the vessels had closed.

The bromsulphalein liver function tests were performed according to the method of Rosenthal⁵. Glycogen in the liver was determined by Pflüger's method⁶.

BLOOD SUGAR

The data recorded in chart 1 represent in every case fasting values, since care was taken to remove all food from the cages and not to feed the animals for at least fifteen hours before blood was drawn for analysis.

For purposes of comparison, the charts have been divided into five groups, namely, those obtained (1) from normal monkeys, (2) from monkeys experimentally infected with yellow fever at a period more than twenty-four hours before death, (3) from ten to twenty-four hours before death, (4) from fifteen minutes to ten hours before death, and (5) at death or not more than five minutes post mortem.

For the large variations between the maximum and minimum values in the first three groups there is no explanation, unless they can be ascribed to differences in the reaction of the individual monkeys to handling. Some of them resisted vigorously when the blood was drawn, while others remained passive. It seems unlikely that the wide normal range of the blood sugar during fasting represents a species peculiarity. The blood sugar falls consistently through the five groups from a normal average of 81 mg per hundred cubic centimeters to 22 mg in those taken at death.

The blood sugar of a number of individual fasting monkeys was determined at definite intervals during the course of the disease. The accompanying table represents the results obtained from some of these

⁵ Rosenthal, S. M., and White, E. C. Clinical Application of the Bromsulphalein Test for Hepatic Function, *J. A. M. A.* **84** 1112 (April 11) 1925.

⁶ Pflüger, E. *Arch. f. d. ges. Physiol.* **119** 119, 1907.

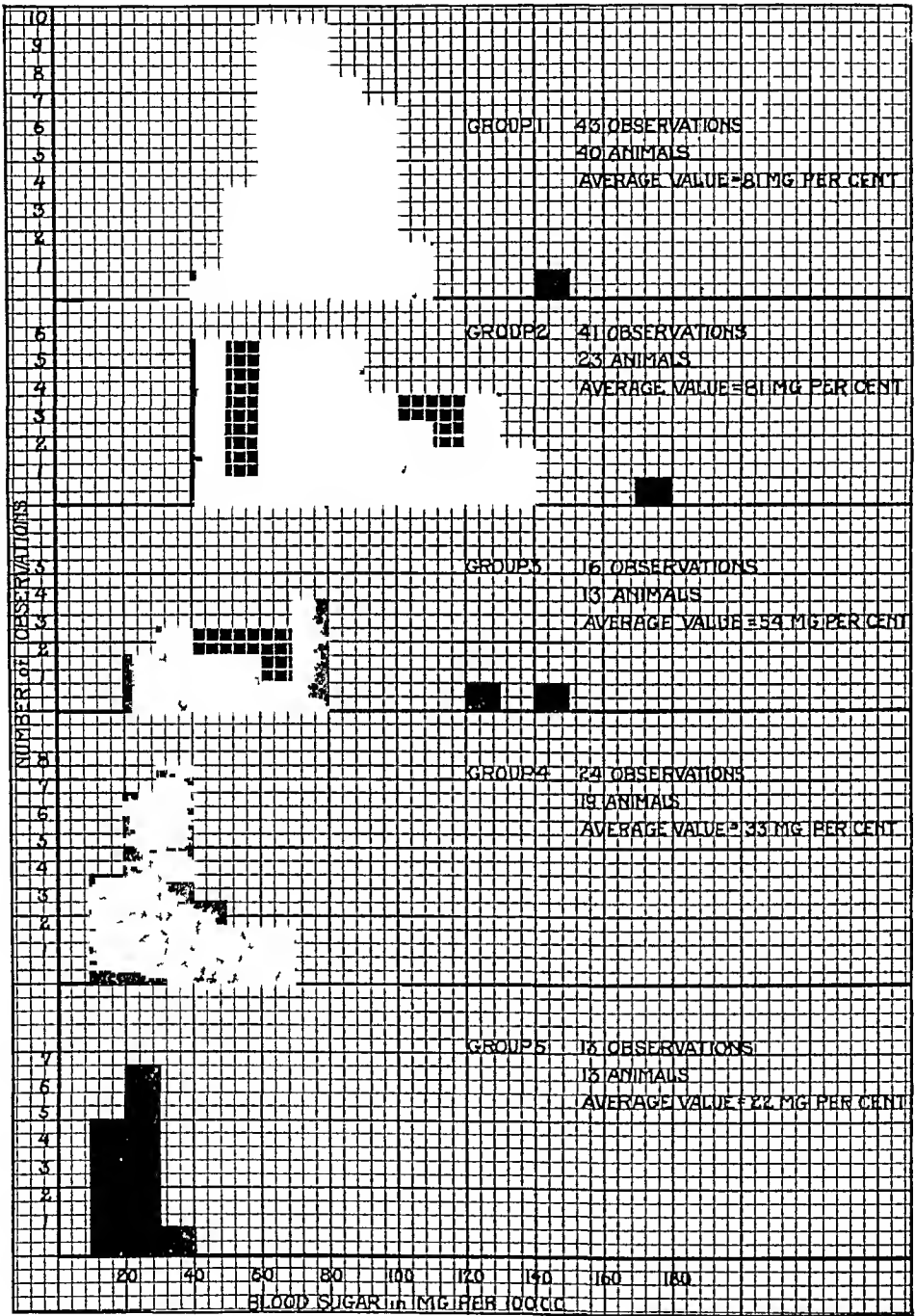


Chart 1—Blood sugar values during fasting during the course of fatal yellow fever in monkeys Group 1, normal monkeys, group 2, monkeys more than twenty-four hours before death, group 3, monkeys from twenty-four to ten hours before death, group 4, monkeys from ten to fifteen minutes before death, group 5, monkeys at time of death or within five minutes after death

cases. A number of long periods of very low blood sugar were observed. *M. rhesus* R1 showed a drop from 123 to 46 mg per hundred cubic centimeters between forty-eight and thirty-nine and one half hours before death. The increase to 58 mg twenty-one hours later is unaccountable. It should be pointed out that values as low as 44 mg

Changes in the Blood Sugar During the Course of Yellow Fever

Monkey	Days After Infection	Number of Hours Before Death	Blood Sugar, Mg per Cent
R 1	3	48 hours 0 minutes	123
	4	39 hours 30 minutes	46
	5	18 hours 30 minutes	58
	6	At death	25
R 1	2	29 hours 0 minutes	95
	3	12 hours 30 minutes	49
	3	7 hours 30 minutes	43
R 11	4	41 hours 30 minutes	77
	5	18 hours 30 minutes	37
	5	12 hours 45 minutes	44
R 15	3	8 hours 0 minutes	31
	3	4 hours 0 minutes	29
	3	2 hours 45 minutes	30
	3	1 hour 0 minutes	28
	3	At death	27
R 16	1	33 hours 0 minutes	62
	2	28 hours 30 minutes	68
	2	9 hours 0 minutes	34
	2	4 hours 30 minutes	30
	3	3 hours 0 minutes	56
	3	At death	25
R 12	2	9 hours 0 minutes	34
	2	3 hours 0 minutes	25
	2	At death	18
R 2	7	50 hours 45 minutes	47
	7	42 hours 45 minutes	37
	8	15 hours 45 minutes	24
R 17	2	60 hours 15 minutes	113
	2	52 hours 15 minutes	75
	3	36 hours 15 minutes	98
	4	12 hours 15 minutes	56
	4	At death	19
R 18	2	26 hours 50 minutes	120
	3	17 hours 20 minutes	64
	3	2 hours 0 minutes	32

were observed in normal fasting monkeys. Nevertheless, a drop from 123 to 46 mg was never observed in the blood of normal monkeys. *M. rhesus* R2 had a blood sugar of 47 mg per hundred cubic centimeters more than fifty hours ante mortem. The figures given in the table clearly indicate that ten hours before death the blood sugar almost invariably reaches hypoglycemic levels. A large number of isolated instances of hypoglycemia at earlier periods were found. For example, the blood sugar of *M. rhesus* R3 was 34 mg twenty and one-half hours before death and that of *M. rhesus* R4, 23 mg twenty-one hours before death.

The lowest blood sugar obtained was 14 mg per hundred cubic centimeters, found in a monkey at death. Usually, although not invariably, when the blood sugar fell below 30 mg the animal was prostrate.

While the blood sugar of monkeys with yellow fever was low during fasting, that of similar monkeys which had been fed shortly before the blood was taken, occasionally showed very high concentrations of sugar. *M. rhesus* R5, while moribund, had a blood sugar of 195 mg per hundred cubic centimeters. Autopsy revealed quantities of food in the stomach, presumably from a meal taken eight hours previously. Blood taken from *M. rhesus* R6, two hours before death and five hours after a meal, contained 286 mg of sugar.

Prolonged periods of low blood sugar failed to produce symptoms of hypoglycemic shock, although many of the monkeys became prostrate. A large proportion of them, although lying down when first seen, would protest vigorously while being handled. Intravenous injection of dextrose during this stage of the disease did not perceptibly improve the condition of the animal. An attempt was made to produce insulin shock in monkeys. Four normal monkeys were used for this purpose. The results of one experiment are given in chart 2. A few minutes after blood from the fasting animal had been obtained for analysis, 5 units of U20 Burroughs and Wellcome's insulin were injected into the right gastrocnemius muscle. Blood samples were taken at intervals and a careful record of the monkey's appearance was made. Although the blood sugar remained below 41 mg per hundred cubic centimeters for at least six hours, and reached a minimum of 23 mg, the animal showed no signs of a hypoglycemic reaction. Two of the other monkeys in this series of experiments showed no reaction, although the blood sugar ranged from 53 to 34 mg for two hours. The fourth animal appeared weak one hour after the intramuscular injection of 30 units of insulin when the blood sugar was 21 mg. Twenty minutes later the animal was lying down, but was able to rise if disturbed. There was definite twitching of the arms and legs. At this time, the blood sugar was found to be 17 mg per hundred cubic centimeters. After an intravenous injection of 1.5 Gm of dextrose, the monkey recovered in fifteen seconds, sat up, defecated, urinated and greedily ate two bananas.

Maddock and Trimble⁷ found that the blood sugar of dogs or of human beings may remain at levels of 50 mg per hundred cubic centimeters or lower for from one to six hours without symptoms, and that such a period may or may not be followed by a hypoglycemic reaction.

7 Maddock, S. J., and Trimble, H. C. Prolonged Insulin Hypoglycemia Without Symptoms, *J. A. M. A.* **91** 616 (Sept. 1) 1928.

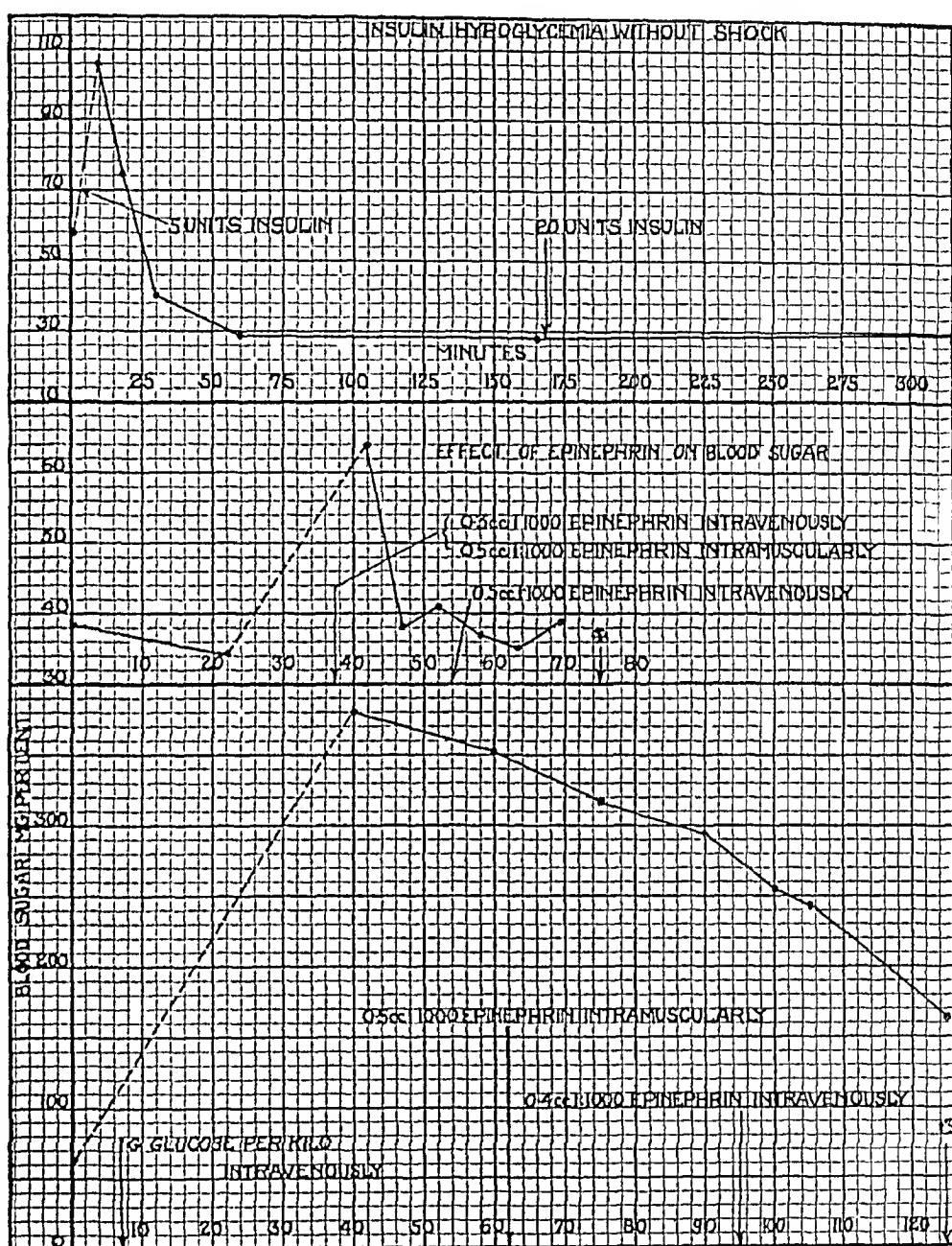


Chart 2—The upper chart shows the influence of insulin on the blood sugar of a normal monkey. The two lower charts illustrate the effects of epinephrine on the blood sugar of monkeys in the terminal, hypoglycemic stage of yellow fever. The middle chart represents the effects of epinephrine given without food, the lowest chart, the effects of epinephrine given after the intravenous injection of dextrose.

In the case of monkeys such behavior was the rule. An unsuccessful attempt was made to determine the amount of nondextrose-reducing substances represented in these low blood sugar values. The only source of yeast available was a batch of bread dough, rich in yeast, containing large amounts of reducing substances which it was not possible to remove, even after twelve washings with distilled water. Cultivation of a pure yeast strain was attempted without success.

LIVER GLYCOGEN

Staining methods have failed to reveal any glycogen in livers of victims of yellow fever after death. Confirmation of these results employing purely chemical methods was desirable. Three monkeys were used for this purpose.

EXPERIMENT 1—From *M. rhesus* R7, 24 Gm of liver was removed two minutes after the animal had died of yellow fever. The liver was cut into moderately small pieces with the scissors and dropped into 25 cc of boiling 60 per cent potassium hydroxide solution. Glycogen was determined according to Pfluger's⁶ procedure. Approximately 10 mg of glycogen per hundred grams of liver tissue was found. The heart blood taken simultaneously with the removal of the liver tissue contained 16 mg per cent of "sugar."

EXPERIMENT 2—*M. rhesus* R8 was bled from the heart while in a moribund condition after one day of fever and one day of subnormal temperature, and 26 Gm of liver was at once transferred to an equal quantity of the hot potassium hydroxide solution. The liver contained 23 mg of glycogen per hundred grams of liver, while the blood sugar was 15 mg per hundred cubic centimeters.

EXPERIMENT 3—*M. rhesus* R9 was killed after two days of fever, when obviously ill but still alive. Fourteen grams of liver tissue was used for analysis. The blood sugar was 19 mg per hundred cubic centimeters, and the liver contained 124 mg of glycogen per hundred grams of tissue.

While it is probable that these monkeys had not eaten for from seven to eighteen hours previously,² nevertheless, from 10 to 124 mg of hepatic glycogen per hundred cubic centimeters is considerably less than would be expected in normal animals deprived of food for a similar period.⁸

The dependence of epinephrine hyperglycemia on the liver glycogen has been demonstrated by Mann⁹ and Markowitz. Mann observed that injections of epinephrine had no effect on the blood sugar of dehepatized dogs, while Markowitz found that subcutaneous injections of epinephrine did not raise the blood sugar of rabbits the livers of which had been rendered glycogen-free by starvation, cold and strychnine. There was a characteristic delay in the appearance of epinephrine

8 Markowitz, J. *Am J Physiol* **74** 22, 1925

9 Mann, F. C. *Medicine* **6** 419, 1927

hyperglycemia in animals the livers of which contained small amounts of glycogen. In the latter animals the resulting hyperglycemia was more or less proportional to the amount of glycogen left in the liver.

Several experiments were performed to determine the effect of epinephrine on the blood sugar of monkeys ill with yellow fever. Two typical experiments will be described.

EXPERIMENT 4—*Macaca mulatta* R10, a female, weighing 3.88 Kg, had been fed on the regular animal house diet. It was inoculated on December 10, it showed a fever on December 12 and a subnormal temperature on the morning of December 13. The animal was used on December 10 and 12 for tests of the liver function and dextrose tolerance tests. At 11:00 a. m. on December 13, the monkey was lying down and appeared to be moribund. Blood samples were obtained from the femoral artery before and after the injection of epinephrine. The results are recorded in chart 2.

About forty-five seconds after the intravenous injection of 0.3 cc. of epinephrine solution, the animal became brighter and moved about slightly. This condition lasted for two minutes and was followed by a return to unconsciousness which persisted until death. A bromsulphalein liver function test made on this monkey one hour before death showed 100 per cent retention of the dye after sixty minutes.

EXPERIMENT 5—*Macaca mulatta* R11, a medium-sized male weighing 2.1 Kg, had also been fed the regular animal house diet. It was inoculated on December 7 and showed fever on December 9, 10, 13, 14 and 15. It had been used on December 12 for a test of the sugar tolerance. On the morning of December 15, the monkey was quite weak but was still sitting up. At 9:15 a. m. 1 Gm. of dextrose per kilogram of body weight was injected intravenously, arterial blood samples were taken at intervals and epinephrine was injected.

The results of the experiment are presented in chart 2. An injection of bromsulphalein was given simultaneously with the injection of dextrose. One and three-fourth hours later, the dye retention was 100 per cent.

It is evident that epinephrine causes less hyperglycemia in monkeys with advanced yellow fever than in normal monkeys.

COMMENT

Of the changes that invariably follow ablation of the liver, hypoglycemia is among the earliest to develop. The blood sugar commences to fall at once after the liver has been removed, and soon reaches a level sufficiently low to produce hypoglycemic shock. Intravenous administration of dextrose is remarkably efficient in relieving the symptoms, and considerably prolongs the lives of the animals. Minkowski¹⁰ observed convulsions and coma in geese, Doyon, Gautier and Policard¹¹ reported convulsions in frogs, after complete removal of the liver. According to Whipple and Hooper,¹² ligation of the hepatic artery in dogs with

10 Minkowski, O. Arch. f. exper. Path. u. Pharmacol. **58** 141, 1908.

11 Doyon, M., Gautier, C., and Policard, A. Compt. rend. Soc. de biol. **64** 271, 1908.

12 Whipple, G. H., and Hooper, C. W. J. Exper. Med. **17** 612, 1913.

Eck fistula produces similar results. Partial removal of the liver of an animal with Eck fistula causes a slight decrease in the blood sugar (Mann and Bollman¹³). A stage is reached, however, after which removal of more liver tissue, short of total hepatectomy, does not lower the blood sugar further.

The regenerative power of the liver and its large factor of safety have been amply demonstrated by numerous investigators. In one experiment designed to elucidate this point, removal of 65 per cent of the liver tissue did not perceptibly change the blood sugar level nor alter the form of the sugar curve following the intravenous injection of dextrose. It is evident that the functional activity of the liver is concerned with maintenance of the normal blood sugar, but that a relatively small proportion of the organ is capable of caring for the needs of the organism in this respect.

It has been demonstrated by the results reported here that blood sugar in animals suffering from yellow fever is greatly reduced, in a few cases, even a day or more before death (chart 1 and table). It is almost certain in the light of previous work on the function of the liver that these low blood sugar values are due to the hepatic lesions accompanying the disease.

Microscopic examination of the liver tissue reveals great variability in the amount of damage in different monkeys early in the febrile period. A few monkeys die without marked changes in the appearance of the liver. However, in a greater number of cases evidence of degeneration is apparent twenty-four hours before death, and it is usually after this time that the blood sugar commences to decrease (chart 1 and table). From then until death there is a progressive fall in the blood sugar level. Almost invariably the degeneration is quite marked twelve hours before death, and it is at this stage that the most significant alterations in the blood chemistry are noticed, particularly in the blood sugar. Failure of urea formation and deamination is a terminal event¹. Although a lowering of blood sugar may occur many hours before abnormalities in the metabolism of urea or amino-acid are evident² (table), this, too, must be considered a terminal event. In the animals that recovered, the blood sugar was never found to be as low as that reported for the average in group 4, chart 1.

The extremely low values found at death are interesting. It is questionable if any of the reducing substance in the blood below 15 mg per hundred cubic centimeters is dextrose. Van Slyke and Hawkins¹⁴

13 Mann, F. C., and Bollman, J. L. Liver Function Tests, *Arch. Path.* **1**: 681 (May) 1926.

14 Van Slyke, D. D., and Hawkins, J. A. *J. Biol. Chem.* **83** 51, 1929.

reported that Benedict's blood sugar method yields an average of about 10 mg per cent of nonfermentable reducing material. Although inability to determine the nonfermentable reducing substances forbids any positive statement, it seems probable that no dextrose or only an insignificant amount is left in the blood of a fasting monkey dying of yellow fever.

Some monkeys' blood sugar was found to be below hypoglycemic levels before they became prostrate. There were none of the customary signs of hypoglycemic shock in these animals, except general weakness and lassitude. However, in only one of four animals did symptoms that produced severe and durable hypoglycemia develop after injections of insulin. It is possible that *M. rhesus* is not so responsive to low blood sugar as are other animals.

While the hypoglycemic reaction induced by removal of the liver is quickly relieved by injections of dextrose, similar treatment did not noticeably improve the condition of animals ill with yellow fever. The situation is complicated by other factors, and probably is comparable to the second stage of shock following hepatectomy, which cannot be relieved by intravenous injections of dextrose.

That blood sugar is dependent on liver glycogen seems evident. Following hepatectomy the blood sugar becomes greatly diminished, and if the liver is made glycogen-free, injections of epinephrine are no longer effective in raising the blood sugar, although in both instances the muscles may contain considerable quantities of glycogen. The low blood sugar found in the later stages of yellow fever also results from a greatly depleted glycogen supply in the liver. Analysis of liver tissue taken from animals in the later stages of the disease revealed practically no glycogen. Only a few milligrams were found in monkeys R7 and R8 when the blood sugar was less than 20 mg per hundred cubic centimeters. Monkey R9, killed while still active after two days of fever and with a blood sugar of 19 mg per hundred cubic centimeters, had 124 Gm of glycogen per hundred grams of liver tissue. While it is doubtful that these monkeys had taken food for twelve hours, the extremely low glycogen content of the liver is probably not due to starvation. Maikowitz⁸ emphasized the difficulty in completely eliminating glycogen from the liver by starvation. The livers of rabbits deprived of food for four days at room temperature still contained from 400 to 480 mg of glycogen per hundred grams.

The effects of injections of epinephrine support the view that the livers of monkeys in the terminal stages of the disease possess little or no glycogen. Maikowitz⁸ found that injections of epinephrine did not raise the blood sugar when the liver was glycogen-free, when only traces

were present, the increase was delayed in proportion to the amount of hepatic glycogen. Monkey R10 showed a sharp brief rise in blood sugar following intramuscular and intravenous injections of epinephrine. An increment of 32 mg per hundred cubic centimeters was observed five minutes after the injection, but five minutes later the blood sugar had returned to preinjection levels. A subsequent intravenous injection of epinephrine did not affect the blood sugar (chart 2). Furthermore, injections of epinephrine did not appreciably alter the rate of fall of blood sugar in *Macaca mulatta* R11 following the intravenous injection of dextrose (chart 2). While it is possible that a slight rise in blood sugar might be masked by the high concentration following the administration of dextrose, nevertheless, an increment of from 10 to 20 mg per hundred cubic centimeters, which persisted an appreciable length of time, would be evident in the shape of the curve.

If the low blood sugar found in the sick monkeys is the result of a greatly depleted supply of hepatic glycogen, the function of glycogenesis was in many cases abolished before there was a failure of deamination or urea formation, for a low blood sugar value (table) was found many hours before significant alterations in blood urea and amino-acid nitrogen were apparent.² McMaster and Drury¹⁵ found that after removal of 70 per cent of the rabbit's liver, convulsions accompanied by a low blood sugar value and death occurred in 33 per cent of their cases without, however, any evidence of disturbances in urea or uric acid metabolism. The results reported previously¹ and those in this paper concur with those of McMaster and Drury, in that the sugar-regulating mechanism was the first to fail. Monkey R12 (table) may be cited as an example, for when the nonprotein nitrogen was 37 mg per hundred cubic centimeters, the urea nitrogen 12 mg, and the amino-acid nitrogen 7 mg the blood sugar had already fallen to 34 mg.

Izume and Lewis¹⁶ suggested that the hypoglycemia following hydrazine intoxication is primarily due to failure of normal glycogenesis. This opinion is apparently substantiated in the case of yellow fever by the abnormally low hepatic glycogen and the abnormally high blood sugar value found in some nonfasting monkeys with yellow fever.

SUMMARY

1 Hypoglycemia was regularly observed in monkeys with yellow fever as early as twenty-four hours before death and became progressively more pronounced as death approached.

15 McMaster, P. D., and Drury, D. R. *J. Exper. Med.* **49** 745, 1929.

16 Izume, S., and Lewis, H. B. *J. Biol. Chem.* **71** 51, 1926.

2 In every case tested the blood sugar during fasting finally fell to a level at which convulsions might have been expected, less than 45 mg per hundred cubic centimeters. Nevertheless, definite symptoms of hypoglycemic shock were not observed, nor did intravenous injections of dextrose have any demonstrable beneficial action.

3 Hypoglycemic shock was difficult to produce in monkeys.

4 After hypoglycemia had appeared, little glycogen was found in the livers of monkeys with yellow fever, and the hyperglycemic action of epinephrine was greatly diminished or abolished.

5 The changes in carbohydrate metabolism definitely preceded the disturbances of deamination and urea formation reported in earlier papers of this series.

THE POTASSIUM CONTENT OF THE HEARTS OF PERSONS DYING FROM EDEMATOUS AND NONEDEMATOUS CONDITIONS *

L C SCOTT, M D

NEW ORLEANS

The inorganic constituents of cardiac muscle and their bearing on cardiac activity have been receiving more and more attention in recent years. The work of Norn¹ on potassium, especially his investigations on the excretion of this element, seems to indicate that the potassium content of the tissues of the normal individual, at least, is constant, and that the body responds promptly to excessive intake by establishing an equilibrium.

At the time of his experiment, Norn had not been able to raise the value of the blood potassium appreciably or for any length of time by administrations of relatively large doses of potassium chloride. Furthermore, to judge from this work, the normal diet furnishes far more potassium than the body can retain and, like sodium salts, that portion not utilized is excreted, principally no doubt, in the urine. The conditions under which the investigations of Norn were carried out were virtually normal.

Goto,² in experiments with animals, showed that acid feeding diminishes the potassium in the muscles, and the analyses of Harrison, Pilcher and Ewing³ on the cardiac and skeletal muscle of patients dying from cardiac disturbances with edema as a symptom sustain their assumption that acidosis of tissue tends to diminish the potassium content. This holds, according to their observations, both for cardiac and for skeletal muscle.

In a series of sixty-nine analyses of cardiac muscle for inorganic constituents, special attention was paid to the potassium and sodium in thirty-two hearts from patients who had died of a variety of diseases.

* Submitted for publication, July 21, 1930.

¹ From the Department of Tropical Medicine, Tulane University of Louisiana.

1 Norn, M I. Untersuchungen uber das Verhalten des Kaliums im Organismus I, Skandinav Arch f Physiol **54-55** 162, 1928-1929, II (in urine), *ibid*, p 185.

2 Goto, Kingo. Mineral Metabolism in Experimental Acidosis, J Biol Chem **36** 366, 1918.

3 Harrison, T R, Pilcher, C and Ewing, G. The Potassium Content of Skeletal and Cardiac Muscle, J Clin Investigation **8** 325 (April 20) 1930.

Fourteen of these patients showed edema of a greater or lesser degree and of varying periods of duration, and eighteen were free from it. Unfortunately, the clinical histories of the majority were obscure and the exact data unobtainable.

All hearts were received almost intact and utilized as soon after autopsy as possible. The determinations of potassium and sodium were made by the method of Finker-Neubauer,⁴ which the original work of Neubauer⁵ shows to be very exact, and which independent determinations with known amounts of potassium and sodium chloride proved to be satisfactory. The details of the methods employed for the determination of these and other inorganic constituents, with the results of the analyses, are explained in an article about to be published.

Not only were a large percentage of the potassium and sodium determinations made in duplicate, but many were repeated four or more times, to test the method thoroughly. In no instance was there reason to doubt the accuracy after experience in manipulation had been attained and when conditions were properly adhered to.

A relation of perhaps more than passing interest, and one certainly not expected, is presented by these analyses. This is that at times the relative preponderance of sodium and potassium is reversed. The reversal is not attributable to inaccurate determinations, since the values often presented close checks, of which the analysis of the heart from patient 127 may serve as an example. The amount of potassium, expressed as K_2O , was found to be the following in a series of seven determinations: 1.284 per cent, 1.252 per cent (three times), 1.251 per cent (twice) and 1.164 per cent. The amount of sodium, expressed as Na_2O , was found to be 0.943 per cent, 0.956 per cent (twice), 1.135 per cent, 0.894 per cent, 0.912 per cent and 0.877 per cent. No other long series of experiments was carried out on any one heart, but four analyses on the basis of 1 Gm. of dry muscle tissue was the usual routine. The others, though checking sufficiently well, did not always yield results as close as those given.

The percentages of water, potassium and sodium stated in the tables are calculated on the basis of cardiac muscle dried to relatively constant weight at 100 C. This furnishes a uniform condition and neutralizes the effect of variability in moisture. In the tabulations, the original percentages of K_2O and Na_2O have been converted into the equivalents of potassium and sodium by multiplying by the factors 0.830 and 0.742.

4 Finker-Neubauer, quoted in Treadwell, Hall. *Analytical Chemistry*, ed. 3, New York, John Wiley & Sons, 1911, vol. 2 pp. 47-48.

5 Neubauer, H. Eine abgekürzte Methode der Kalibestimmung in den Kalisalzen, *Ztschr. f. analyt. Chem.* **39**, 481, 1900.

In table 1 are presented the fourteen analyses of hearts from patients dying of diseases in which edema was one of the symptoms. The following brief outlines are taken from data obtained in the ward and the Pathological Department.

CASE 96—For J. B., no clinical history was obtainable. Edema of unknown duration was mentioned on the history sheet. There was evidence of edema of both extremities, especially of the right side, and of the penis and scrotum. The clinical diagnosis was congestive heart failure. The anatomic diagnosis was bronchopneumonia, chronic myocarditis, hypertrophy and dilatation of the heart, acute and chronic nephritis and chronic splenitis.

CASE 102—C. R.'s edema began two years before the present study with general swelling of the lower extremities. The face later became swollen. The

TABLE 1—Results of Analyses of Cardiac Muscle from Patients with Edema

Patient	Sex	Age	Analysis of Cardiac Muscle*			Disease
			Moisture, per Cent	Potassium, per Cent	Sodium, per Cent	
96	M	65	80.93	0.668	1.017	Congestive heart failure
102	M	22	79.65	1.163	0.910	Congestive heart failure
103	M	66	78.06	0.670	0.883	Diabetes, gangrene
106	M	65	80.47	0.591	0.603	Arteriosclerotic heart disease
108	M	40	78.38	0.579	0.899	Congestive heart failure
109	M	80	78.84	0.871	0.808	Arteriosclerotic heart disease
110	M	60	80.76	0.886	0.863	Congestive heart failure, syphilis
111	M	62	80.57	0.781	0.826	Congestive heart failure
114	M	41	81.12	0.944	0.969	Congestive heart failure
115	M	42	79.90	1.026	0.917	Syphilitic heart disease
116	M	56	79.17	1.184	1.059	Congestive heart failure
122	M	42	80.95	1.107	0.941	Congestive heart failure
123	F	36	80.22	1.183	0.880	Chronic nephritis, congestive heart failure
126	M	72	81.25	1.089	0.717	Congestive heart failure, chronic nephritis
Mean			80.02	0.910	0.878	
Standard deviation			1.011	0.215	0.112	
Probable error			±0.710	±0.150	±0.080	

* Results for potassium and sodium expressed on the basis of dry muscle tissue from the left ventricle.

edema eventually became so severe that the patient was sent to the hospital. The clinical diagnosis was circulatory failure. The anatomic diagnosis was lobar pneumonia of the lower left lobe (bilateral and fibrinous), pleuritis (localized), interlobar empyema (right side), purulent pericarditis, acute nephritis and fatty degeneration of the liver.

CASE 103—J. G. suffered from constant pain in the feet. These pains increased gradually, and the patient noticed that his toes were drying up. The history mentioned edema of the feet and legs. The clinical diagnosis was diabetes mellitus. The anatomic diagnosis was gangrene of the right foot and left toe, and toxemia.

CASE 106—H. W.'s clinical history was not available. Edema was present over the legs. The clinical diagnosis was arteriosclerotic heart disease. The anatomic diagnosis was carcinoma of the stomach, chronic nephritis, generalized arteriosclerosis, hypertrophy of the heart, aneurysm of the ascending portion of the arch of the aorta and bilateral hydrothorax.

CASE 108—About one month before admission to the hospital, E. P. suffered from dizziness and shortness of breath, with disturbed vision. Edema of the

legs and thighs existed during the period in the hospital. The clinical diagnosis was hypertension, chronic myocarditis with decompensation, marked secondary anemia and auricular fibrillation. The anatomic diagnosis was acute and chronic nephritis, hypertrophy and dilatation of the heart, brown atrophy of the lungs, bilateral hydrothorax and fatty degeneration of the liver.

CASE 109—No clinical history was available for B. J. The left lower leg was edematous. The clinical diagnosis was chronic varicose ulcer of the leg. The anatomic diagnosis was bronchopneumonia, acute and chronic nephritis, arteriosclerosis, acute splenitis, fatty degeneration of the liver and chronic myocarditis.

CASE 110—The clinical history for I. H. stated that about four months before admission to the hospital the patient noticed swelling of his feet and legs. The clinical diagnosis was chronic myocarditis with decompensation, hypertension, inguinal adenitis and syphilis. The anatomic diagnosis was bronchopneumonia (bilateral), acute and chronic nephritis, chronic myocarditis, splenitis and atrophic gastritis.

CASE 111—Three weeks before admission to the hospital, J. D. woke up to find his feet swollen and painful. The clinical diagnosis was chronic myocarditis with decompensation and chronic nephritis. The anatomic diagnosis was lobar pneumonia, empyema, bilateral gangrene, arteriosclerosis, syphilis, cirrhosis of the liver, aortitis and chronic nephritis.

CASE 114—Marked edema of the legs and abdomen was mentioned in the history of R. B. About a year before the patient noticed swollen feet. The clinical diagnosis was congestive heart failure, hypertensive heart disease, chronic nephritis and probable aneurysm (dilatation of the arch). The anatomic diagnosis was syphilitic aortitis, erosion of the aortic valve, acute and chronic nephritis, passive congestion of the liver and spleen and fibrous pleuritis.

CASE 115—T. H. had extensive edema of the right side of the body. No clinical history was available. The clinical diagnosis was syphilitic heart disease and aortitis. The anatomic diagnosis was acute and chronic myocarditis (syphilitic), acute and chronic nephritis with cystic degeneration, aortitis, endocardial sclerosis (aortic and mitral valves), passive congestion of the spleen, edema and congestion of the lungs.

CASE 116—In E. L.'s case, edema was present over the legs and thighs. The duration was about three weeks. The clinical diagnosis was decompensation. The anatomic diagnosis was bilateral bronchopneumonia, hypertrophy and dilatation of the heart, chronic nephritis and passive congestion of the liver and spleen.

CASE 122—No clinical history was available for J. W. Marked edema was noted. The clinical diagnosis was congestive heart failure. The anatomic diagnosis was chronic myocarditis with dilatation and hypertrophy, bronchopneumonia, general anasarca, passive congestion of the kidneys and spleen and cirrhosis of the liver.

CASE 123—M. G. had edema of the legs the duration of which had been about four weeks. During this time, the condition became so bad that she was unable to recline at night. The clinical diagnosis was hypertensive heart disease, chronic nephritis, congestive heart failure and auricular fibrillation. The anatomic diagnosis was acute and chronic parenchymatous nephritis, chronic myocarditis with hypertrophy, pulmonary infarctions of the right lung, passive congestion of the liver and spleen, hydrothorax on the right side, acute fibrinous pleurisy (right lung) and atelectasis of the right lung.

CASE 126—The ankles of H R were slightly edematous Two years before, he became dyspneic, but did not grow materially worse until three weeks before admission to the hospital, then he noticed that his ankles were slightly edematous The clinical diagnosis was senility, syphilis, partial heart block, chronic nephritis and chronic myocarditis with decompensation The anatomic diagnosis was multiple abscesses of the kidneys, pyelonephrosis (bilateral), carcinoma of the gallbladder, chronic myocarditis, aortitis, passive congestion of the liver, early cirrhosis of the liver, congestion of the spleen, acute cystitis, pulmonary congestion and edema and hypertrophied prostate

Table 2 contains the analyses of eighteen hearts from patients whose disease processes were not productive of an edematous condition The clinical diagnoses only are given

TABLE 2—*Results of Analyses of Cardiac Muscle from Patients Without Edema*

Patient	Sex	Age	Analysis of Cardiac Muscle*			Disease
			Mo s ture, per Cent	Potas sium, per Cent	Sodium per Cent	
97	M	47	78.92	0.785	0.854	Tuberculosis, lobar pneumonia
98	M	70	78.17	0.891	0.938	Lobar pneumonia
99	F	39	79.55	0.891	0.872	Carcinoma
100	M	40	80.92	0.769	1.002	Lobar pneumonia
101	F	17	82.12	1.155	0.832	Tuberculous meningitis
104	M	47	80.32	0.707	0.872	Lobar pneumonia
105	M	51	82.12	0.851	1.178	Pulmonary tuberculosis
107	M	60	79.80	0.621	0.845	Lobar pneumonia, syphilis
112	M	13	77.25	0.937	0.915	Syphilis, bronchopneumonia
113	M	19	84.91	0.726	1.306	Pulmonary tuberculosis
117	M	64	79.99	1.110	0.743	Arteriosclerotic heart disease
118	F	34	80.95	0.709	1.134	Carcinoma
119	M	24	81.29	1.061		Lobar pneumonia
120	M	54	80.65	0.992	1.190	Pulmonary tuberculosis
121	M	82	80.23	0.620	0.549	Bronchopneumonia, arteriosclerosis
124	M	49	79.11	1.316	0.815	Miliary tuberculosis
125	M	22	80.42	1.467	0.699	Bronchopneumonia
127	F	33	80.56	1.041	0.813	Pellagra
Mean			80.30	0.925	0.915	
Standard deviation			1.518	0.229	0.188	
Probable error			±1.040	±0.160	±0.131	

* Results for potassium and sodium expressed on the basis of dry muscle tissue from the left ventricle

COMMENT

There is considerable variation in the values for both potassium and sodium regardless of whether or not the patient suffered from edema prior to death, and the final averages do not indicate any appreciable difference in the cardiac content The average of fourteen hearts from edematous patients for potassium is 0.910 per cent and for those of eighteen persons who did not have edema 0.925 per cent, while the results for sodium were, respectively, 0.878 per cent and 0.915 per cent

Nor is there a marked difference in the water content, those with edema having an average of 80.02 per cent and those without 80.30 per cent An edematous condition of the wall of the heart, whatever state the skeletal tissues may be in, apparently does not usually exist

Sections of fresh cardiac muscle were subjected to Macallum's⁶ sodium cobaltrinitite method for demonstrating the potassium within the cell and interstitial spaces. There can hardly be any doubt, if one may judge from the distribution of the stain, that the greater part of the potassium is localized in the intercellular spaces. In the cell itself, the potassium appears to be uniformly diffused throughout the protoplasm. The striations become very distinct, and Macallum stated that potassium is condensed in the dark bands and in the middle third of the latter when the fiber is contracted.

CONCLUSIONS

1 The results of analysis of thirty-two hearts for potassium and sodium do not seem to indicate that there is on an average any appreciable difference in the amount of these elements in hearts from edematous and from nonedematous patients.

2 The water content is practically the same for both categories.

3 There is considerable variation in the amount of potassium and sodium in hearts, regardless of whether the disease processes from which the patients died were or were not productive of edema.

4 The percentage of sodium may be greater than that of potassium and vice versa without any apparent relation to disease.

5 Demonstration of potassium in cardiac tissue indicates that the larger proportion of the salts is contained in the fluid bathing the muscle cells, and that they are rather uniformly diffused throughout the protoplasm.

⁶ Macallum, A. B. On the Distribution of Potassium in Animal and Vegetable Cells, *J. Physiol.* **32**: 95, 1905.

THE BLOOD LIPOIDS IN NEPHROSIS AND CHRONIC NEPHRITIS WITH EDEMA^{*}

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The old clinical classification of subacute or chronic diffuse nephritis (chronic parenchymatous nephritis) with edema, and its pathologic counterpart, the large white kidney, has been superseded by the present day concepts of chronic nephrosis and the nephrotic phase of glomerulonephritis, developed from the work of F Muller, Munk, Volhard and Fahr, A A Epstein and others. The clinical picture of pure or uncomplicated nephrosis has been repeatedly defined in recent years (principally in the German and American literatures) as one of profuse albuminuria, edema, oliguria, insidious onset, normal concentrating power of the kidney, prolonged course with tendency to cyclic remissions and low basal metabolic rate (occasional), with absence of cardiovascular changes, such as hypertension, retinitis, hematuria or uremia. Furthermore, it is widely maintained that chronic nephrosis manifested by degenerative changes in the kidney tubules, without demonstrable glomerular lesions, in adults at least, is an uncommon condition, that, much more frequently, the nephrotic syndrome represents a phase of varying duration in the natural history of glomerulonephritis, a phase in which, for the time, the functional changes ordinarily associated with glomerular disease may be entirely overshadowed and arterial hypertension may be absent. Although rare in adults, pure nephrosis is not uncommon in young children (Schwarz and Kohn¹). Since the investigations of A A Epstein,² it is generally known that the fundamental changes in the composition of the blood in nephrosis consist in (1) lowering of the serum proteins, affecting the albumin fraction more than the globulin, so that there is a tendency toward inversion of the

^{*} Submitted for publication, July 23, 1930

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1 Schwarz, H, and Kohn, J L. Studies of Nephritis in Children. I. Nephrosis, *Am J Dis Child* **24** 125 (Aug) 1922, Bacteremia and Skin Manifestations in Lipoid Nephrosis, *ibid* **38** 762 (Oct) 1929

2 Epstein, A A. *J Exper Med* **20** 334, 1914, The Nature and Treatment of Chronic Parenchymatous Nephritis (Nephrosis), *J A M A* **69** 444, 1917, *Am J M Sc* **163** 167, 1922, *Arch f Verdauungskr* **44** 31, 1928

albumin-globulin ratio, (2) increase in the lipid content of the plasma. Correlated with the increase in plasma lipoids is the presence of double refractile bodies in the urine (Munk³) and deposits of double refractile lipoids in the kidney tubules shown to be cholesterol esters. Whether or not nitrogen retention is a feature depends on the incidence of glomerular lesions.

It is of the chemical features that we wish to speak, and especially of the increased lipoids of the blood plasma in clinical nephrosis.

Blood Chemistry in Nephrosis and Chronic Nephritis with Edema

Case	Date	Plasma Lipoids					Phos phatide, Mg per Cent (P x 26)	Serum Proteins, Gm per Cent			Urea Nitrogen, Mg per Cent
		Cholesterol, Mg per Cent			Ester per Cent of Total	Albu min		Glob ulin	Total		
		Free	As Ester	Total							
Nephrosis											
1	10/23/29	235	390	625	62						
	11/ 1/29	285	715	1,000	72	335	2.0	2.9	4.9	9	
	11/19/29	150	835	985	85	442	1.1	2.7	3.8	7	
	1/ 7/30					382					
	4/25/30			960		325	1.5	3.5	5.0		
2	11/10/29			960		652					
	12/ 2/29	185	500	685	73	419	2.0	2.8	4.8	9	
3	7/19/29	390	220	610	36		2.7	3.0	5.7	15	
	7/31/29	45	405	450	90		3.7	2.8	6.5		
4	10/22/29			350		273	4.8	2.1	6.9	8	
5	11/14/29	160	190	350	54	317					
	11/29/29	50	270	320	84	274	3.4	1.1	4.5	92-224	
Chronic nephritis with edema											
6	11/11/29			360		263			5.8	10	
7	1/10/30	55	300	355	84	326				43	
8	4/10/30			550		369	2.2	3.1	5.3	7	
9	7/22/29	210	540	750	72						
	7/29/29	450	550	1,000	55		1.6	1.4	3.0	20-30	
	7/31/29	30	780	810	96						
10	2/ 4/30			450		353	1.6	2.2	3.8	23	
	4/11/30			440			1.9	2.3	4.2	25	
11	4/11/30			1,140		395	1.7	2.2	3.9	14	
	5/4/30	615	375	990	38		2.8	1.2	4.0	24	
12	5/ 9/30			1,380			2.2	2.3	4.5	10	
	5/14/30	50	870	920	95	450	2.5	2.8	5.3	10	
13	11/11/29	105	235	340	69	426			7.0	188	
	11/23/29	210	250	460	54	442					
Nephrosis in remission											
14	1/ 9/30	85	125	210	60	176	3.2	2.4	5.6	15	
15	2/ 1/30			200		208	5.7	2.1	7.8	13	

During the past year we have had the opportunity in the medical and pediatric services of the hospital to make complete chemical studies in twelve cases of nephrosis and chronic glomerulonephritis with edema, including the estimation of the cholesterol, cholesterol esters and phosphatides in the blood plasma.⁴ The data are presented in the accompanying table.

³ Munk, F. *Ztschr f klin Med* **78** 1, 1913.

⁴ Cholesterol, free and combined, estimated by the method of Blco. and Knudson (*J Biol Chem* **27** 107, 1916), phosphatides by a modification of the method of Kuttner and Cohen (*ibid* **75** 517, 1927) and Kuttner and Lichtenstein (*ibid* **86** 671, 1930), and serum proteins by the method of Wu (*ibid* **51** 33, 1922).

Port,⁵ in 1910, and shortly afterward Chauffard, Laroche and Grigaut,⁶ reported an increased cholesterol content in the serum of certain patients with chronic nephritis. Since then increases in the cholesterol content of the blood have been observed by numerous investigators in cases of clinical nephrosis and the nephrotic type of glomerulonephritis (chronic parenchymatous nephritis with edema in the old terminology) but not in other types of nephritis (Denis⁷ and Bloor⁸). Greenwald⁹ made the observation that the plasma lipid phosphorus is often increased in nephritis. Daniels¹⁰ found a substantial increase in plasma lecithin in five of seven cases of chronic parenchymatous nephritis, as well as an increase in fatty acids and cholesterol. Increased concentration of plasma lecithin was also observed by Oser and Karr¹¹ in several cases of uremia. Knauer¹² pointed out that in nephrosis, in addition to the cholesterol, the phosphatides and fatty acids are consistently increased in amount, he also observed that with an exacerbation of the disease, the lipoids rise and then decline with clinical improvement, and that in cases of acute hemorrhagic nephritis the total amount of lipoids is not increased above the normal values. Daniels¹⁰ likewise found that in the forms of renal disorder examined other than chronic parenchymatous nephritis, no comparable increase of plasma lipoids was found. Recently, Gainsborough¹³ in a study of twenty cases of "so-called lipid nephrosis" reported a consistent increase in the total cholesterol content of the blood, but principally in that fraction combined with fatty acids, the cholesterol esters. We were able to confirm these observations (accompanying table).

The lipoids of the blood plasma were estimated in twelve cases of clinical nephrosis, as were the serum proteins and urea nitrogen in most instances. Among these were three cases (cases 1, 2 and 3), all of them in children, that seemed to conform strictly to the criteria for lipid nephrosis, one case of syphilitic nephrosis (case 4), a case of amyloid disease of the kidneys (case 5), and seven cases (cases 6 to 12) in which a nephrotic picture supervened in the course of subacute or

5 Port, F. *Deutsches Arch f klin Med* **99** 259, 1910

6 Chauffard, A, Laroche, G, and Grigaut, A. *Compt rend Soc de biol* **70** 108, 1911

7 Denis, W. *J Biol Chem* **29** 93, 1917

8 Bloor, W R. *J Biol Chem* **31** 575, 1917

9 Greenwald, I. *J Biol Chem* **21** 29, 1915

10 Daniels, W B. *Brit J Exper Path* **6** 283, 1925

11 Oser, B L, and Karr, W G. *The Lipoid Partition in Blood in Health and in Disease*, *Arch Int Med* **36** 507 (Oct) 1925

12 Knauer, H. *Med Klin* **23** 840, 1927

13 Gainsborough, H. *Quart J Med* **23** 101, 1929

chronic glomerulonephritis. A case of renal rickets (case 13) was studied which showed an appreciable increase in blood lipoids, of the same order of magnitude as that regularly observed in nephrosis, but which nevertheless presented none of the other features of nephrosis. In addition, several children formerly observed with clinical nephrosis were studied when their condition was in the stage of remission and showed complete restoration of normal lipid partition of the blood (cases 14 and 15).

REPORT OF CASES

CASES 1, 2 and 3—These cases occurred in children under 4 years of age. A diagnosis of lipid nephrosis was made. The course was characterized by persistent albuminuria and cyclic periods of edema, in which the blood lipoids were regularly increased and the serum proteins diminished. There was no history of hematuria, hypertension, etc. These cases seemed to conform in all respects to the criteria for lipid nephrosis.

CASE 4—In a man known to have syphilitic aortitis, syphilitic nephrosis developed while he was under observation. Edema of the ankles, persisting for a year, was accompanied by copious albuminuria. Double refractile bodies were found in the urine. The absence of hypertension, hematuria or nitrogen retention was noted. The patient was discharged in an improved condition.

CASE 5—Amyloid kidneys, with secondary contraction and terminal uremia occurred in a patient, a man with a long-standing case of tuberculosis of the hip. The diagnosis was confirmed by autopsy.

CASES 6, 7 and 8—These cases in children all showed features of nephrosis: copious albuminuria, edema and lipoidemia. Because of hematuria at some time and in one instance (case 7) transient hypertension and moderate nitrogen retention, these cases must be regarded as presenting a nephrotic picture supervening in the natural history of acute glomerulonephritis.

CASES 9, 10, 11 and 12—In these cases, the patients were adults, with clinical histories of marked, persistent and recurrent edema and profuse albuminuria. These cases were regarded clinically as presenting a nephrotic picture developing in the course of subacute or chronic glomerulonephritis, because hematuria, hypertension or diminished concentrating ability was present.

CASE 13—This case occurred in a child, aged 6, with renal rickets. The patient had severe rickets, not improved by treatment, and nephritis that was evidenced by marked nitrogen retention (urea nitrogen, 188 mg), but there were no uremic symptoms. The blood lipoids were increased, especially the phosphatides.

CASES 14 and 15—The children had been observed in previous attacks of clinical nephrosis and were now in a state of remission. These cases are cited to exemplify the normal lipid distribution in blood plasma.

COMMENT

The previous observations of an increase in cholesterol, fatty acids and phosphatides in blood plasma were abundantly confirmed. In our series of cases both the total cholesterol and the phosphatide values were uniformly increased, in the most marked instances to a strikingly high

level, e g , cholesterol 1,380 mg per hundred cubic centimeters¹⁴ The phosphatide content of the blood plasma was regularly elevated, with the increase most marked in cases with the highest cholesterol values and a low amount of serum proteins

A striking feature of this general lipoidemia is the increase of cholesterol esters observed in the circulating blood In six cases, from 80 to 90 per cent of the total cholesterol was combined with fatty acids In the remaining instances, although the ratio of ester cholesterol to total cholesterol was lower, the absolute increase in the ester fraction was nevertheless significant

As previously cited, Gainsborough¹³ in a study of a series of cases of "so-called lipid nephrosis" found a consistent increase in the total cholesterol content of the blood, but principally in that fraction combined with fatty acids In several instances, just as in our series, this increase in cholesterol ester obtained to a much smaller degree The significance of an increase in the fatty acid content of the blood (Daniels, Knauer) is difficult to interpret, since the fatty acids estimated after saponification may be derived from many sources neutral fat, phosphatides or cholesterol esters On the other hand, the finding of a decided increase of cholesterol esters in the circulating blood may be correlated with their presence in the urine of nephrotic patients as double refractile bodies and with their deposition in the renal tubules

A diminution of the serum proteins, particularly of the albumin fraction, was observed to be regularly associated with the lipoidemia, and the tendency in many quarters is to regard both phenomena as concomitant features of an underlying generalized metabolic disorder, imperfectly understood The experiments of Fishberg and Fishberg,¹⁵ who produced lipemia in rabbits by prolonged bleeding, suggested that the lipoidemia is a compensatory mechanism for the loss of protein, in the maintenance of the osmotic pressure of the blood This hypothesis, however, would not explain the occasional case of clinical nephrosis in which the cholesterol values of the blood seem to show no definite relation to the level of serum proteins or to the occurrence of edema, nor would it explain the lipoidemia (as in case 13) that may occur in chronic nephritis with normal serum proteins and no edema

14 Through Dr George Baehr, we have had the opportunity of studying a case of chronic lipid nephrosis in a 17 year old girl in whom the blood cholesterol, which on admission was 700 mg per hundred cubic centimeters of plasma, rose to the extraordinary figure of 2,200 mg, coincident with the administration of thyroxine After the discontinuation of the treatment, the cholesterol regressed to 850 mg per hundred cubic centimeters

15 Fishberg, E H, and Fishberg, A M Proc Soc Exper Biol & Med 25 296, 1928, Biochem Ztschr 195 20, 1928

A slight but definite increase, both in the total cholesterol and phosphatide values of the blood was further observed in three of five cases of chronic nephritis, in the stage of terminal uremia. The lipid increases were hardly of the order of magnitude of those observed in nephrosis, nor were we able to correlate them with conspicuous damage to the kidney tubules in the sections observed post mortem. In contradistinction to this, all of the five cases of acute nephritis studied gave values within the normal ranges.

Finally, increases in the free and combined cholesterol and in the phosphatide content of blood plasma are encountered in subacute or chronic glomerulonephritis with edema, as well as in so-called lipid nephrosis, without demonstrable glomerular changes. In fact, the lipidemia and the changes in serum protein in chronic diffuse nephritis with edema may in many instances be as pronounced as they are in nephrosis. The chemical picture may be so similar that a differentiation is made possible only by the history, the presence of erythrocytes in the urine, hypertension, changes in the fundus and cardiovascular involvement.

SUMMARY

- 1 Chemical studies of the blood plasma (cholesterol, cholesterol ester, phosphatides, serum proteins and urea nitrogen) were made in three cases of lipid nephrosis, one instance of syphilitic nephrosis, one instance of amyloid nephrosis and seven cases of chronic glomerulonephritis with edema. In all of them, increased values were found for cholesterol, both total and ester, and for phosphatides.

- 2 The cholesterol ester fraction was found to be consistently increased—in six cases up to from 80 to 90 per cent of the total cholesterol. This observation may be correlated, in considering the pathogenesis of nephrosis, with the presence of cholesterol esters in the urine (double refractile bodies) and in the kidney tubules.

- 3 In most instances the lipidemia was associated with a diminution of the serum proteins, especially of the albumin fraction.

- 4 The seven patients with chronic glomerulonephritis with edema likewise showed lipidemia. The increase in total cholesterol, cholesterol esters and phosphatides was as striking as that observed in cases of nephrosis.

TERMINAL HYPOGLYCEMIA^{*}

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WITH THE COOPERATION OF

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BALTIMORE

The introduction of microchemical methods into the laboratories of hospitals has made available a fertile field for scientific investigation which has been attended by notable progress in the knowledge concerning many of the fundamental processes of life. This has been particularly true in regard to carbohydrate metabolism, and, while an increased content of blood sugar has been a familiar clinical phenomenon, the introduction of insulin therapy has focused attention on the hypoglycemic condition—a condition more frequent than was formerly supposed.

The present work was started some time ago as a study of the chemical constituents of the blood at death and one hour after death. The purpose of the investigation was to study the value of postmortem blood chemistry, particularly in cases in which an autopsy is not obtainable, and to study the chemical changes that might take place in the blood constituents during the hour immediately following death. Especial attention was given to the blood sugar and any changes it might undergo, because of the practical as well as the scientific value and also because of the possible medicolegal significance. The specimens of blood were obtained by cardiac puncture immediately, or within ten minutes, after death and one hour after death. Since the corpuscles of the postmortem heart blood frequently settle, all chemical determinations were made on the plasma by the usual hospital methods,¹ although frequently there was insufficient material for a complete analysis.

The concentrations of sugar and urea in the blood and in the plasma are essentially the same, although, as is well known, the plasma chlorides are considerably higher than the chlorides of the blood, and the plasma amino-acid nitrogen is somewhat lower.

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¹ Benedict, S R. *J Biol Chem* **68** 759, 1926. Karr, W G. *J Lab & Clin Med* **9** 329, 1924. Folin, O. *J Biol Chem* **51** 377, 1922. Whitehorn, J C. *J Biol Chem* **45** 449, 1921. Haden, R L. *Clinical Laboratory Methods*, ed 2, St Louis, C V Mosby Company, 1924. Thannhauser, S J and Anderson, E. *Arch f klin Med* **137** 179, 1921.

The data are given in the accompanying table. The most interesting and suggestive observations to cause sudden alarm were the frequent low terminal amounts of sugar in the blood or the plasma, which seemed to indicate that hypoglycemia was a complicating factor in the death of a large percentage of the cases. Thus among thirty-three unselected cases, taken as opportunity permitted, there were twelve cases, or 36 per cent, that showed low blood or plasma sugars, ranging from 28 to 75 mg per hundred cubic centimeters at the moment of death. These surprisingly low values for sugar were totally unexpected since none of these patients had received insulin or any other antihyperglycemic substance, nor were there any obvious clinical reasons or symptoms to indicate hypoglycemia. The diagnoses of the cases in the table were taken from the patients' charts and were primarily clinical, although a few were confirmed by autopsy. Extended clinical discussions and protocols hardly seem warranted as the present series is too small to serve as a basis for an exhaustive theoretical discussion.

The hypoglycemic condition appears to develop rapidly. Thus ten hours before death the patients in cases 1 and 2 had blood sugars of 129 and 140 mg per hundred cubic centimeters of blood, whereas, at death the plasma sugars were 50 and 38 mg respectively. The patient in case 11 had a terminal plasma sugar of 50 mg, whereas three hours before death the blood sugar had been 90 mg. That a definite hypoglycemia existed before death is proved by cases 6, 7, 8 and 5 in which the values for blood sugar (obtained by venipuncture) were 28, 31, 33 and 55 mg at periods of one-half, one-half, one and four hours, respectively, before death, and the sugar values of the plasma of the heart blood were essentially the same at the time of death. The blood sugar apparently decreases uniformly throughout the body, as indicated by case 8, in which, one hour before death, there was a blood sugar of 33 mg (by venipuncture), and at death, of 29 mg, the corresponding plasma sugar taken from the heart at the same time was 33 mg.

An explanation of these unexpected observations is difficult. Nadler and Wolfer² stated that spontaneous hypoglycemia may be caused by hyperinsulinism³ with excessive utilization of sugar, or a deficiency in the storage of glycogen or mobilization of sugar in the function of

2 Nadler W H, and Wolfer, J A. Hepatogenic Hypoglycemia Associated with Primary Liver Cell Carcinoma, *Arch Int Med* **44** 700 (Nov.) 1929.

3 Wilder, R M, Allan, F N, Power M H, and Robertson H E. Carcinoma of the Islands of the Pancreas, *J A M A* **89** 348 (July 30) 1927. Harris, S. Hyperinsulinism and Dysinsulinism *J A M A* **83** 729 (Sept 6) 1924. Thalhimer, W, and Murphy, F D. Carcinoma of the Islands of the Pancreas. Hyperinsulinism and Hypoglycemia, *J A M A* **91** 89 (July 14) 1928. Allan, F N. Hyperinsulinism, *Arch Int Med* **44** 65 (July) 1929. Allan, F N, Boeck, W C, and Judd, E S. The Surgical Treatment of Hyperinsulinism, *J A M A* **94** 1116 (April 12) 1930.

The Chemical Constituents of the Blood Before, At and One Hour After Death

Case	Time Before Death, Hours	Sugar, Mg		Urea, Mg		Ammonia nitrogen, Mg		Carbon Dioxide, per Cent		Sodium Chloride, Mg		Bilirubin, Mg		Age	Diagnosis	
		Before	After	Before	After	Before	After	At	After	At	After	At	After			
1	10	129	50	47	64	62	8.4	8.8	29	29	640	646	3.0	58	Chronic alcoholism, syphilis, arterio-sclerotic disease	
2	10	140	38	25	92	145	10.0	9.7	29	30	518	502	4.7	26	Chronic alcoholism, hepatitis, toxic jaundice, delirium tremens	
3	10	105	75	66	10	36	6.0	6.1	34	33	510	513	2.5	55	Chronic alcoholism, hepatic cirrhosis, edema of the lungs	
4	4	69	62	60	55	67	6.0	6.7			593	576	0.3	11	Lupoid nephrosis, ascites, subacute pancreatitis	
5	4	55												75	Uremia secondary anemia	
6	1/2	28	25		405									67	Uremia, arteriosclerosis, cardiac dilatation	
7	1 1/2	31	30		46	40	29.0	30.2					0.3	52	Chronic dilatation of the stomach with partial intestinal obstruction	
8	1	33	33	29									0.3			
9	20	125	61		40	40	8.0	8.8					0.4	16	Miliary tuberculosis	
10			31				10.5	11.1						30	Postoperative, intestinal obstruction, acute dilatation of the stomach	
11	3	90	50		73								0.7	60	Traumatic amputation of right leg	
12	22	100	50	44	40	33								67	Postoperative, intestinal obstruction	
13	40	160	148	85	85	80	15.6	16.0						67	Pulmonary edema, anemia	
14	30	170	200	180	114	215	8.8	9.2						75	Bilateral bronchopneumonia	
15	116	116			230								18.0	33	Septicemia, toxic hepatitis	
16	48	138	100		70	130	11.0	11.5			619	602	10.0	71	Hypertrophied prostate, bronchopneumonia	
17	40	130	164	121	14	48	6.1	8.0	60	37	600	605		60	Bronchopneumonia	
18	21	119	100	88	99	160	5.8	6.1	10	7	637	651	21	21	Lobar pneumonia	
19	5	164	182	179	46		10.2	11.4	48	42	605	609		60	Chronic alcoholism, bronchopneumonia, pachymeningitis	
20	19	116	128	118	49	54	9.3	10.0	32	26	667	672		36	Chronic alcoholism, periodic paralysis	
21	40	119	123	108	58	54	6.3	6.6						37	Peritonitis	
22	43	109	154	50	207	140	5.4	9.3	42	20	610	606		30	Bichloride nephrosis, bronchopneumonia	
23	37	95	139	131	60	102	6.7	7.0	46	43	544	539	3.4	24	Lobar pneumonia	
24	15	125	190	182	200	330	10.4	9.7	18	20	594	561	3.8	52	Lobar pneumonia	
25	8	121	121	105	400	452	6.0	6.7	34	26	635	627		67	Uremia	
26	25	211	187	180	108	110	6.1	6.1	46	38	7.0	759		23	Pregnancy, cesarean section, cerebral thrombosis	
27	60	130	166	32	50	80	6.7	8.2	42	21	600	555		29	Empyema lobar pneumonia	
28	10	144	190	174	130	180	8.2	10.0	26	10	520	522		38	Typhoid fever	
29	40	111	118	111	81	116	7.8	7.4			666	660		74	Bilateral bronchopneumonia	
30	46	182	219	200	216	228	7.0	7.6						30	Syphilis, hernia obstruction	
31	22	142	138	132	93	85	5.3	5.7			610	607		50	Bronchopneumonia	
32	20	116	108	103	77	89	6.1	6.7						51	Bronchopneumonia	
33	30	127	118	109	92	90	5.9	6.0						49	Peritonitis	

the liver, but it appears difficult to believe that hyperinsulinism could be involved in all of the foregoing cases because the histories do not reveal any previous attacks of hypoglycemia. As will be noted in the table, at least three of the patients had obvious involvement of the liver, and it has been well demonstrated that complete removal of the livers of dogs results in a rapid fall in blood sugar.⁴ Low blood sugars have also been observed in rare cases of gross hepatic disorders, such as acute yellow atrophy⁵ or carcinoma of the liver. However, the patients in cases 1 to 3 do not seem to present sufficiently severe hepatic disease to account for such low amounts of sugar, since many patients having greater damage to the liver have been seen with normal blood sugars. Even though in cases of hepatogenic pathology such low terminal sugar values are not so surprising, it is more difficult to explain the low sugar values found in cases 4 to 9, which were diagnosed as nephrosis, uremia, empyema, carcinoma of the stomach and military tuberculosis, respectively. In these cases there was no apparent evidence of injury to the liver although, as Allan⁶ pointed out, the liver may still be at fault and it is conceivable that one function may fail while other functions remain intact. The point is difficult to prove. Cases 10, 11 and 12 presented postoperative conditions in which hypoglycemia seemed to develop suddenly. Again we have no explanation to offer except to point out that there may be some relation between postoperative shock and spontaneous hypoglycemia.

During recent years various interesting types of hypoglycemia have been described. Thus certain relations between vitamin deficiency and hypoglycemia,⁷ spontaneous hypoglycemia,⁸ compensatory hypoglycemia after the ingestion of sugar,⁹ vagotonia and hypoglycemic reactions,¹⁰ hypoglycemia in hepatic disorders and eclampsia, as well as chloroform or carbon tetrachloride poisoning with resultant increase in guanidine values,¹¹ severe pulmonary tuberculosis and hypoglycemia,¹² typhano-

4 Mann, F. C. *Medicine* **6** 419, 1927.

5 Schmidt, E. G. The Amino-Acid Content of the Blood in Health and in Disease, *Arch. Int. Med.* **44** 351 (Sept.) 1929. Rabinowitch, I. M. *J. Biol. Chem.* **83** 333, 1929.

6 Allan (footnote 3, fourth reference).

7 Sure, B., and Smith, M. E. *J. Biol. Chem.* **82** 307, 1921. Guicher, S. *Arch. f. d. ges. Physiol.* **203** 365, 1924.

8 Ashe, B. I., Mosenthal, H. O., and Ginsburg, G. *J. Lab. & Clin. Med.* **13** 109, 1927. Pettersson, A. S. *Acta med. Scandinav.* **69** 232, 1928.

9 Levine, V. E. *Proc. Soc. Exper. Biol. & Med.* **24** 627, 1927.

10 Nielsen, J. M. *J. Nerv. & Ment. Dis.* **63** 456, 1926.

11 Watanabe, C. K. *J. Biol. Chem.* **33** 253, 1918, **34** 51, 1918. Bodansky, M. *Am. J. Physiol.* **66** 375, 1923. Minot, A. S., and Cutler, J. T. *J. Clin. Investigation* **6** 369, 1928, *Proc. Soc. Exper. Biol. & Med.* **26** 607, 1927. Titus, P., and Dodds, P. *Am. J. Obst. & Gynec.* **15** 303, 1928.

12 Barack, M., Wowski, P., and Ranzman, G. *Beitr. z. Klin. u. Tuberk.* **65** 769, 1927.

somiasis and hypoglycemia in guinea-pigs¹³ infectious disease of rabbits and hypoglycemia with fatty degeneration of the liver,¹⁴ etc., have been studied from various angles. However, none of the authors draws attention to or explains the great frequency of hypoglycemia found among hospitalized patients, as indicated by the data in the table.

It is interesting to note that the patients in cases 5, 9 and 11, although receiving a 5 per cent dextrose Murphy drip, had low amounts of blood sugar, a condition that appears to demonstrate the futility of this type of therapy as a source of available carbohydrate for the organism. In fact, Pressman¹⁵ recently showed that following the introduction of dextrose into the rectum, the blood sugar level falls without a preliminary rise, and he pointed out that dextrose is usually given by rectum to patients in whom sugar depletion is likely to occur, and that the status of sugar deficiency would then be aggravated rather than improved by the administration of sugar via the rectal route.

Although no diabetic patients are included in this study, many of the patients showed a definite hyperglycemia, none of this group had received dextrose, except those in cases 13, 14, 16 and 21, who had been receiving dextrose Murphy drips. However, as previously pointed out, this type of administration of sugar does not seem to produce an elevation in the level of the blood sugar. In a number of cases hyperglycemia was quite marked and ranged from 130 to 219 mg. at the time of death. This great variety in terminal sugars, ranging from 25 to 219 mg., again demonstrates the marked instability of the equilibrium of blood sugar in the patient who is desperately ill.

In general, only a very small decrease in the blood sugar took place during the hour immediately following death. However, there were two noteworthy exceptions. Thus in case 22—a case of mercuric chloride nephrosis and bronchopneumonia—the blood sugar decreased from 154 to 50 mg., and in case 27—a case of empyema and lobar pneumonia—the sugar decreased from 166 to 32 mg. during the hour following death. It is difficult to explain these marked decreases in the postmortem sugar content of the blood. Most of the remaining cases, several having the same diagnosis, showed but a slight decrease during the same interval and under the same conditions. As this work was nearing completion, the significant work of Paul,¹⁶ and that of Pucher and Burd,¹⁷ who found that the plasma sugar frequently was low from

13 Dubois, A. *Compt rend Soc de biol* **99** 656, 1928.

14 Oppel, W. W. *Ztschr f d ges exper Med* **60** 86 1928.

15 Pressman, J. *Am J M Sc* **179** 520, 1930.

16 Paul, J. R. *Ayer Clinical Laboratory of the Pennsylvania Hospital, Philadelphia, October, 1925, Bull* **9**.

17 Pucher, G. W., and Burd, L. A. *Bull Buffalo General Hospital, April, 1925*.

one-half to two hours after death. Paul suggested that hypoglycemic states must be relatively common in the terminal or agonal stages of a large variety of conditions.

It was found that the plasma urea frequently increased rapidly during the last few hours of life. Thus in case 2, the blood urea rose from 92 to 150 mg during the ten hours prior to death. However, there was little change in the urea during the hour after death, and a specimen taken during that time gave a true picture of the content of blood urea at the time of death.

It has recently been shown that the amino-acid nitrogen of the blood remains constant in health and in disease,¹⁸ however, the data in the table indicate a frequent terminal increase in aminonitrogen, which continues to increase after death. Cases 8 and 10 show a particularly high content of aminonitrogen, which is difficult to explain, since there were no signs of hepatic insufficiency or any other condition that might result in such marked amino-acidemia. The carbon dioxide-combining power of the plasma was determined in a few cases, and small decreases were usually noted during the postmortem hour, whereas the chlorides remained constant during the same interval. It might be interesting to point out that in cases 22 and 27 in which there was such marked decrease in the postmortem sugar during the hour following death there was a corresponding marked decrease in the carbon dioxide-combining power of the plasma and an unusually large increase in aminonitrogen. This chemical syndrome indicates a rapid cadaveric decomposition but there seems to be no apparent reason why these unusual changes should have taken place since all of the bodies were treated alike, i. e., allowed to remain in the death bed during the hour of postmortem study.

SUMMARY

1 Blood chemistry determinations have been made before, at and one hour after death, on thirty-three nondiabetic patients dying in the hospital.

2 Among these thirty-three unselected cases, twelve cases, or 36 per cent, showed low terminal blood or plasma sugars, ranging from 28 to 75 mg per hundred cubic centimeters at the moment of death.

3 In a number of cases it was demonstrated that this pronounced and suggestive hypoglycemia existed before death as well as at death.

4 Only a slight decrease was noted in the blood sugar during the hour immediately following death, although there were two note-

18 Schmidt (footnote 5, first reference)

worthy exceptions in which the sugar of the heart blood decreased from 154 to 50 and from 166 to 32 mg during the first postmortem hour

5 The blood urea frequently increased rapidly just prior to death, but little change took place after death

6 Frequently there was a terminal rise in amino-acid nitrogen, which continued to increase somewhat after death. The carbon dioxide-combining power of the plasma decreased somewhat shortly after death, but the chlorides remained unchanged

LIVER EXTRACT FOR PERNICIOUS ANEMIA

BLOOD CHANGES DURING THE FIRST MONTH, REPORT OF
ONE HUNDRED AND ONE CASES¹

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The daily ingestion of large amounts of mammalian liver ($200 \pm$ Gm of prepared weight daily), together with a well balanced diet, has been shown by Minot and Murphy¹ to benefit essentially all patients with pernicious anemia. Following this epoch-making discovery, Cohn and Minot and their associates - prepared, by means of chemical fractionation, certain fractions of liver which were fed to patients with pernicious anemia. Minot and Murphy had previously accumulated data relative to the reticulocyte (young red blood cell) response and the rate of red blood cell formation in those patients fed liver. This knowledge therefore served as a means of eliminating ineffective fractions and of estimating the potency of active fractions. A water-soluble, nitrogenous, nonprotein extraction of liver, known as "fraction G," was obtained, a few grams of which were as effective in the treatment for pernicious anemia as were large quantities of whole liver.

In order to make this therapeutic agent available, various fractions of liver were manufactured for the Pernicious Anemia Committee of the Harvard Medical School by Eli Lilly and Company. Liver extract no 343, which closely resembled "fraction G," was selected by the committee for general distribution after satisfactory clinical evidence had been accumulated through the cooperation of a number of test clinics scattered in widely separated sections of the country.

Minot, Cohn, Murphy and Lawson³ reported on the use of this standardized product, no 343, in the treatment of eighty-nine patients

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* From the Lilly Laboratories for Clinical Research, Indianapolis City Hospital

1 Minot, G R, and Murphy, W P. Treatment of Pernicious Anemia by a Special Diet, *J A M A* **87** 470 (Aug 14) 1926, A Diet Rich in Liver in the Treatment of Pernicious Anemia, *ibid* **89** 759 (Sept 3) 1927

2 Cohn, E J, Minot, G R, Fulton, J F, Ulrichs, H F, Sargent, F C, Weare, J H, and Murphy, W P. *J Biol Chem* **74** 69 (July) 1927. Cohn, E J, Minot, G R, Alles, Gordon A, and Salter, W T. *J Biol Chem* **77**, 325 (May) 1928

3 Minot, G R, Cohn, E J, Murphy, W P, and Lawson, H A. *Am J M Sc* **175** 599 (May) 1928

with pernicious anemia When given daily in such amounts as were derived from 300 to 600 Gm of liver (from 9 to 18 Gm of the extract),⁴ there was observed a rapid regeneration of the red blood cells and a striking improvement in the health of the patients

The use of adequate daily amounts of liver or effective fractions of liver for the treatment of patients with pernicious anemia has since been well established by numerous investigators in this country⁵ and in foreign countries⁶ Sufficient time has now elapsed for one to say that effective fractions of liver have produced more than a temporary improvement in the blood and in the health of patients with pernicious anemia and have simplified the treatment of patients with this disease

The problem of standardizing and determining the potency of fractions of liver containing the active principle or principles cannot as yet be determined or even estimated by chemical or biologic methods Likewise, true pernicious anemia cannot as yet be produced by experiment in animals, consequently, it is necessary to determine the relative potency of these fractions by feeding approximately a maximal daily amount to patients with pernicious anemia who are in relapse and who have no complications

The data recorded by Minot, Cohn, Murphy and Lawson relative to the production of the maximum number of reticulocytes, as observed and calculated, and the rate of red blood cell formation when patients with pernicious anemia were fed maximal daily amounts of liver extract no 343 serve as a standard by which various lots of liver extract or other therapeutic agents employed for the same purpose may be evaluated

It is my purpose in this paper to record additional data obtained when liver extract no 343, made under the direction of the Committee on Pernicious Anemia, was employed and data obtained subsequently up

4 Minot, Cohn, Murphy and Lawson (footnote 3) have estimated that the loss in the preparation of the standardized extracts from whole liver probably does not exceed 30 per cent

5 Heath, E H Pernicious Anemia Treated with Liver Diet and Liver Extract, *J A M A* **91** 928 (Sept 29) 1928 Ordway, T, and Gorham, L W The Treatment of Pernicious Anemia with Liver and Liver Extract, *J A M A* **91** 925 (Sept 29) 1928 Middleton, W S The Erythropoietic Response of the Various Anemias to Liver Therapy, *J A M A* **91** 857 (Sept 22) 1928 Richardson, W New England *J Med* **200** 540 (March 14) 1929 Sturgis, C C, Isaacs, R R, and Smith, M *Ann Int Med* **1** 983 (June) 1928

6 Muelengracht, E *Ugeskr f læger* **90** 408 (May 3), 123 (Feb 9) 1928 Greenacher, K E *Zentralbl f inn Med* **49** 1178 (Dec 15) 1928 Schulten, H *Munchen med Wchnschr* **76** 1281 (Aug 2) 1929 East, C F T *Brit M J* **1** 491 (March 24) 1928 Jogic, N, and Spengler, G *Wien klin Wchnschr* **40** 1480 (Nov 24) 1927

to the present time. Information on various fractions of liver made during the period of early production and prior to the production of the standardized product is also included. These other fractions were similar to extract no. 343, but varied in potency to a greater extent than did the standardized product.

There is little information reported in this paper which has not been presented in the exhaustive work of Minot and his associates, however, these observations, made on a series of controlled patients, confirm and add to that which has already been reported.

CLINICAL MATERIAL AND METHODS

In this series 101 patients with typical primary pernicious anemia were studied over a period of from one month to three years. Sixty-one of these patients were fed adequate daily amounts of the standardized liver extract no. 343, and were treated at a time when their initial red blood cell counts ranged between 0.53 and 3.27 million per cubic millimeter of blood and averaged 1.64 million.

There were twenty-five additional patients, whose red blood cell counts before treatment averaged 1.7 million per cubic millimeter of blood, who were fed various experimental fractions of liver similar to liver extract no. 343; however, only the rate of red blood cell production at the end of one month's treatment has been reported in this paper. Information relative to the production of reticulocytes has been purposely omitted, although, in many instances, it compared favorably with that observed when extract no. 343 was administered.

There were fifteen patients treated with the standardized liver extract no. 343 when their initial red blood cell counts were above 3 million per cubic millimeter and averaged 3.4 million.

On admission to the hospital, each patient was studied for the purpose of establishing the diagnosis of pernicious anemia. Control data relative to the formed elements in the blood, the percentage of hemoglobin (Newcomer method) and blood bilirubin determinations were made. The reticulocyte counts were made from fixed cover-glass preparations of capillary blood stained with brilliant cresyl blue and counter-stained with Wright's stain. The percentage of reticulocytes was based on the number observed in counting 1,000 red blood cells, and very high or very low counts were checked. The absolute number of reticulocytes per cubic millimeter of blood was calculated by multiplying the number of red blood cells by the percentage of reticulocytes that occurred at the same time. In the majority of cases, daily observations of the blood were made during the first three or four weeks of treatment with monthly observations thereafter.

Data were excluded when the percentage of reticulocytes was high (above 3 per cent) before treatment as a result of the ingestion of liver, blood transfusions, complicating factors such as infectious processes or as a result of spontaneous remissions. The data obtained after the first month of treatment will be reported in a separate paper.

RESPONSE OF THE RETICULOCYTES AT VARIOUS RED BLOOD CELL LEVELS

In table 1 are recorded the results obtained when maximum daily amounts of the standardized liver extract no. 343 were fed to sixty-one patients with pernicious anemia, whose red blood cell counts immediately before treatment was begun ranged between 0.53 and 3.27 million per cubic millimeter of blood. The absolute number of reticulocytes before treatment was begun at the peak of their rise and at the end of the third week has been recorded.

There was a distinct tendency for the number of reticulocytes observed at the peak of their rise to be greater, the lower the red blood cell count before treatment, so that approximately an inverse relation existed. Individual variations, however, were observed.

In nearly every instance the number of reticulocytes in the blood at the end of the third week of treatment was greater than the number observed before treatment was begun.

In case 58, 58A and 58C three separate and distinct relapses occurred because of the omission of liver extract, and, in each instance, reticulocyte responses were obtained when treatment with adequate daily amounts of liver extract was resumed.

The characteristics of the reticulocyte responses were typical of those described by Minot and his associates and others for patients fed adequate daily amounts of potent fractions of liver. As a rule, the first increase in the absolute number of reticulocytes was observed about the fourth day after treatment was begun. The peak of the rise (the greatest absolute number of reticulocytes) was reached usually between the eighth and ninth days, after which there was a gradual decrease. Approximately three weeks were required to complete the reticulocyte response, that is, from the beginning of their increase until the number approached that found normally in the blood.

RESPONSE OF THE RETICULOCYTES TO VARIOUS DAILY AMOUNTS OF LIVER EXTRACT NO. 343

The maximum number of reticulocytes delivered into the circulation at the peak of their rise was influenced by the daily amount of potent fractions of liver administered.

TABLE 1—*The Number of Reticulocytes at the Peak of Their Rise and the Red Blood Cell Counts at the End of Approximately One Month of Treatment When Approximately Maximal Daily Amounts of the Standardized Fraction of Liver No 343 Were Fed to Sixty-One Patients with Pernicious Anemia During Relapse*

Case	Sex	Age	Reticulocytes in Millions per C Mm			Red Blood Cells in Millions per C Mm	
			Before Treatment	At Peak of Rise	End of Third Week	Immediately Before Treatment	End of Approximately One Month
36	F	68	0.055	0.61	0.012	0.53	2.00*
26	M	10	0.005	0.51	0.085	0.55	3.57
33	M	69	0.002	0.60	0.100	0.63	3.54
3	M	51	0.021	0.52	0.065	0.91	3.53
21	M	71	0.018	0.45	0.076	0.92	3.00
78	F	55	0.031	0.33	0.009	0.99	3.06
88	F	55	0.019	0.52	0.027	0.99	3.34
16	J	68	0.005	0.10	0.123	1.00	3.24
65	F	12	0.013	0.31		1.04	3.00
59	F	27	0.033	0.40		1.05	3.23
14	F	50	0.050	0.61	0.025	1.08	4.06
6	F	45	0.008	0.33	0.023	1.08	3.67
71	M	67	0.020	0.56	0.074	1.12	
97	I	55	0.026	0.48	0.068	1.15	3.63
106	I	63	0.028	0.41	0.064	1.16	3.33
11	F	26	0.036	0.63	0.093	1.17	3.71
66	F	55	0.008	0.30	0.065	1.17	3.90
12	M	66	0.021	0.21	0.071	1.18	3.16
72	M	71	0.060	0.45	0.060	1.30	3.56
83	M	50	0.023	0.45	0.028	1.30	3.68
8	I	27	0.010	0.37	0.061	1.32	
92	M	71	0.021	0.42	0.032	1.32	3.50
2	M	58	0.022	0.41	0.081	1.34	3.97
91	M	62	0.020	0.60	0.060	1.34	4.32
90	M	42	0.003	0.55	0.115	1.36	3.96
10	F	59	0.020	0.38	0.117	1.38	3.48
108	F	16	0.016	0.29	0.042	1.40	
20	M	16	0.031	0.27	0.110	1.41	3.52
11	M	66	0.010	0.20	0.018	1.43	3.82
98	M	51	0.012	0.33	0.114	1.43	3.50
28	F	51	0.031	0.33	0.053	1.44	3.39
22A	M	48	0.032	0.22	0.011	1.41	3.00
61	J	51	0.013	0.30	0.120	1.46	3.59
19	M	52	0.006	0.56	0.007	1.50	3.40
9	M	52	0.017	0.57	0.017	1.55	3.69
75	M	66	0.029	0.52	0.083	1.55	3.69
75	M	70	0.036	0.47	0.064	1.55	3.02
68	M	57	0.021	0.21	0.057	1.56	3.61
68	M	55	0.016	0.52		1.64	3.68
24	M	29	0.025	0.53	0.116	1.67	4.17
77	F	61	0.015	0.14	0.055	1.76	3.87
99	M	59	0.009	0.16	0.014	1.78	3.87
101	M	68	0.017	0.21	0.026	1.80	3.27
111	F	38	0.022	0.39		1.80	
58A	F	55	0.011	0.32	0.112	1.81	3.33
56	F	65	0.038	0.28	0.057	1.92	3.05
58C	F	55	0.031	0.26	0.061	1.93	3.00
51	M	49	0.005	0.29	0.065	1.97	4.18
25	F	37	0.020	0.35	0.049	2.08	3.15
23	M	18	0.016	0.65		2.09	
17	M	41	0.015	0.39	0.063	2.15	3.55
103	M	51	0.010	0.22		2.18	3.77
110	F	60	0.025	0.14	0.069	2.20	3.51
95	M	58	0.021	0.25	0.056	2.21	3.47
46	M	11	0.037	0.25	0.061	2.23	3.49
62	M	60	0.069	0.13	0.087	2.23	3.36
42	M	62	0.011	0.12		2.32	3.67
15A	F	43	0.017	0.22	0.026	2.37	3.44
99	M	57	0.016	0.15	0.013	2.44	3.36
60	M	60	0.002	0.12	0.011	2.63	4.35
41	F	60	0.027	0.08	0.015	2.99	3.36
72	M	61	0.019	0.12	0.058	3.06	3.67
41	M	53	0.023	0.076		3.27	3.60

* This patient had a persistent diarrhea during the entire month of treatment and was given 4 cc of dilute hydrochloric acid three times daily without relief. Failure to absorb a sufficient amount of the active principle probably accounted for the low red blood cell count at the end of the first month of treatment.

In table 2 are recorded observations made during the treatment of twenty-six patients with pernicious anemia whose red blood cell counts immediately before treatment were at similar levels and were below 3 million per cubic millimeter of blood

The amount of active principle derived from 100 Gm of liver, when given daily to one patient for twenty-eight days, was not sufficient to produce a reticulocyte response or an increase in red blood cells. When the same total amount of extract (112 Gm) was fed at the rate of 12 Gm daily (extract derived from 300 Gm of liver) to the same patient, a prompt increase in reticulocytes and red blood cells was obtained on the seventh day. (See case 1A, table 1)

In those patients who received the active principle derived from 300 Gm of liver daily, a slightly submaximal number of reticulocytes was produced at the peak of their rise, and the day on which the peak

TABLE 2—*Data Concerning Twenty-Six Patients Receiving Liver Extract No. 343 in Various Daily Amounts*

Number of Cases	Daily Amount of Standardized Extract Derived from Liver, in Gm	Average Number of Days to Reticulocyte Peak	Average Number of Reticulocytes at Peak of Their Rise, in Millions per C Mm	Average Number of Red Blood Cells in Millions per C Mm		
				Before Treatment	End of First Month	Gain, End of First Month
1	100	No increase in 28 days		1.3	1.4	
6	300	10.3	0.307	1.0	3.5	2.5
6	400	9.0	0.380	1.3	3.3	2.0
6	600	8.0	0.396	1.5	3.4	1.9
7	800-1,000	7.0	0.399	1.3	3.3	2.0

occurred was somewhat later than when amounts derived from 400 to 1,000 Gm of liver were fed. Essentially a maximum number of reticulocytes was produced when the active principle obtained from 400 Gm of liver was given daily. Greater amounts of the active principle did not produce an appreciable increase in the average number of reticulocytes at the peak of their rise. The velocity of the reticulocyte response, however, was increased so that the average day of the peak was reached sooner. The increased velocity of the reticulocyte response had little advantage from a practical point of view, since the red blood cell counts for the various groups reached about the same level at the end of the first month of treatment.

At the present time, fractions of liver are being clinically tested for potency by giving a slightly submaximal amount of liver extract daily (that derived from 300 Gm of liver). It is believed that this permits a more critical test than when maximal daily amounts are administered.

RATE OF PRODUCTION OF RED BLOOD CELLS

The rate of production of red blood cells was largely dependent on the number of reticulocytes delivered into the circulation when the level

of the red blood cells before treatment was below 3 million per cubic millimeter of blood. Those factors which have been shown to influence the magnitude of the reticulocyte response, such as the level of the red blood cells before treatment and the daily ingestion of maximum amounts of potent fractions of liver, have in turn influenced to a great extent the rate of red blood cell production.

In table 1 the red blood cells at the end of the first month of treatment averaged for the group of 61 patients, 3.5 million per cubic millimeter of blood. The data in table 3 include the averages for the red blood cells before treatment and at the end of one month for the various groups which comprised the total number of 101 patients treated.

The groups of patients whose average initial red blood cell counts were below 3 million per cubic millimeter reached an average level of

TABLE 3—*Increase in Red Blood Cells at the End of Approximately One Month of Treatment with Liver Extract No. 343 and Other Comparable, Potent Fractions of Liver*

Number of Cases	Range of Red Blood Cells in Millions per C Mm Before Treatment	Average Red Blood Cell Count per C Mm in Millions		
		Immediately Before Treatment	End of Approximately One Month's Treatment	Gain, End of Approximately One Month's Treatment
8	0.73 to 1.0	0.78	3.45	2.67
30	1.0 to 1.5	1.22	3.52	2.30
20	1.5 to 2.0	1.71	3.56	1.82
16	2.0 to 2.5	2.22	3.48	1.26
12	2.5 to 3.0	2.73	3.62	0.89
9	3.0 to 3.5	3.30	4.01	0.71
6	3.5 to 4.8	3.71	4.30	0.59

approximately 3.5 million at the end of the first month of treatment, although there were individual variations above or below 3.5 million, some of which are shown in table 1.

The rate of red blood cell production during the first month of treatment is useful in attempting to evaluate the potency of a given therapeutic agent especially when combined with information relative to the production of reticulocytes at the peak of their rise.

The gain in the average number of red blood cells at the end of the first month for the various groups was in inverse relation to the average level of the red blood cells before treatment was begun.

In the groups of patients with initial red blood cell counts below 3 million per cubic millimeter, the reticulocyte responses accounted for the greater gains in red blood cells observed, whereas the groups with initial red blood cell counts above 3 million showed smaller gains, and no apparent increase in the number of reticulocytes was seen in the blood stream.

OTHER CHANGES IN THE BLOOD

Myelocytes and nucleated red blood cells of various types were frequently observed in the blood, especially preceding or during the period in which the reticulocytes appeared in greatest numbers. During this period and sometimes immediately following it, the white blood cells increased from leukopenic levels to normal or greater than normal with an absolute increase in granulocytes. A leukocytosis which occasionally reached from 12,000 to 15,000 per cubic millimeter of blood was seen in many instances. The occurrence of eosinophilia, reported in natural remissions and in those produced by the feeding of liver, was not observed in the series of patients fed liver extract.

The blood platelets were decreased in number during relapse and were abnormal in their histologic appearance. During the reticulocyte response they also increased, as time passed, usually to numbers greater than normal. Later they regained their usual morphologic appearance and approached the number found normally in the blood.

The hemoglobin increased at a slower rate than the red blood cells in most instances, so that the color index usually dropped below 1 in from three to five weeks. In the patients who produced the greatest number of reticulocytes on the day of the peak of their rise, the color index decreased most rapidly, often reaching 1 or below by the end of the second week. The color index remained above 1 in the patients who showed the slowest increase in red blood cells and in most of the patients with pronounced neurologic manifestations, even though their red blood cells had reached normal levels.

The majority of the patients had an increase in blood bilirubin during relapse, which decreased rapidly in all of the cases and usually faster in the cases with the greatest reticulocyte responses. The patients who had unsatisfactory reticulocyte responses because of too little extract did not experience a decrease in their blood bilirubin. The blood bilirubin became normal, or less than normal, by the end of the first two or three weeks.

CLINICAL IMPROVEMENT

The degree of clinical improvement following an adequate response of the red blood cells has been described by numerous investigators, so that it has become a matter of common knowledge, suffice it to say, that, with the exception of those patients who had or developed complications during the first month of treatment, striking clinical improvement was observed and the general health of the patients was materially benefited.

SUMMARY

One hundred and one patients with typical pernicious anemia were treated with potent fractions of liver. Sixty-one of these patients were

given adequate daily amounts of a standardized fraction of liver, no 343. The results obtained relative to the production of reticulocytes are in accord with those reported by Minot and his associates. The maximum number of reticulocytes produced at the peak of their increase was influenced by the level of the red blood cells before treatment was begun and by the daily amount of potent extract of liver ingested.

In uncomplicated cases, the amount of extract (approximately 12 Gm.) derived from 300 Gm. of liver produced a slightly submaximal number of reticulocytes on the day of the peak, however, the number of red blood cells produced at the end of one month was essentially the same as that produced when larger daily amounts of extract (that derived from 400 to 1 000 Gm. of liver) were given.

The average gain in red blood cells at the end of one month's treatment for the entire series of 101 patients bore an inverse relation to the level of the red blood cells before treatment was begun. In the patients whose red blood cell counts were below 3 million per cubic millimeter of blood before treatment, the count reached approximately a level of 3.5 million at the end of one month.

The number of reticulocytes produced at the peak of their rise, combined with information relative to the rate of red blood cell production for the first month of treatment, seems a useful means of determining the potency of fractions of liver.

Miss Helen Chandler gave me much technical assistance.

GASTRIC AND DUODENAL ULCER IN THE BLACK PEOPLE OF ABYSSINIA *

STUART BERGSMA, M D

ADDIS ABABA, ABYSSINIA

Gastric and duodenal ulcer is generally regarded as a rare condition among Negroes¹. One of the standard systems of surgery² contains the records of the New Orleans Board of Health for ten years. In the decade cited, gastric ulcer caused 0.123 per cent of the deaths among the white population, but only 0.043 per cent of those among the Negroes, of 6,800 medical cases in white persons there were 58 (0.086 per cent) of gastric ulcer, whereas of 4,900 medical cases in Negroes there were only 2 (0.004 per cent) of gastric ulcer, i. e., there were approximately twenty times as many cases in the white population as in the black. A recent statistical summary of the Bellevue Hospital, New York, from 1904 to 1922 gave a total of 120 cases of gastric ulcer, of which only 2 were in Negroes. Forty-four cases of duodenal ulcer were recorded, none of which were in Negroes³. Frank cited 2 cases of duodenal ulcer and 1 of gastric ulcer which were personally seen by him, he described the condition as rare⁴.

This, however, is not true of the black people of Abyssinia, among whom gastric and duodenal ulcer is a relatively common disease. Peculiarly enough, acute appendicitis in an Abyssinian is a distinct rarity. According to information from personal conversation with other physicians in Abyssinia, not a single case of acute appendicitis has been seen in an Abyssinian. As usually stated, one is led to believe that there is something in the black race itself which makes gastric and duodenal ulcer an unusual occurrence in Negroes in the United States. That this is not the fact and that other factors must be sought among the black people of the United States of America is my contention in this article when I stress the relative frequency of the disease among the black people of Abyssinia.

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From the American Mission Hospital

1 Lewis, Dean. Practice of Surgery, Hagerstown, Md, W. F. Prior Company, Inc., 1928, vol. 6, chap. VI, p. 5

2 Keen. Surgery, Philadelphia, W. B. Saunders Company, 1921, vol. 4, pp. 1145 and 1142

3 Sturtevant, M., and Shapiro, L. L. Gastric and Duodenal Ulcer, Frequency, Number, Size, Shape, Location, Color, Sex and Age, in 7,700 Necropsy Records at Bellevue Hospital, Arch. Int. Med. **38**: 41 (July) 1926

4 Frank, L. W. Duodenal Ulcer in a Negro, Kentucky M. J. **20**: 74, 1922

Abyssinia is a very new country in a surgical sense. Until approximately six years before the present writing, there was not a single surgical hospital in Abyssinia, and it has been only within the last four years that any considerable number of major operations have been performed. But what has impressed me at the two largest hospitals in Abyssinia (hospitals with only seventy and thirty beds, respectively) is the relatively great number of the black people whose chief complaint is "stomach trouble" of several years' duration. It has proved an entire waste of time and medicine to attempt to treat any of the patients with gastric or duodenal ulcer by diet and alkaline treatment similar to that of Sippy, even in selected acute cases. While in the hospital, the patient does well on a milk diet and alkalis, and experiences complete relief from pain and hyperacid burning. He is discharged in good condition with sufficient medicine for several weeks and fails to report at the clinic. A few months later he returns, again very miserable, having neglected to take any powders after his first day out of the hospital and having returned to his native diet within a few days of leaving the hospital. Since this diet consists of a sour bread, an extremely peppery sauce and raw meat, and since milk is practically unobtainable, it is manifestly impossible to control gastric and duodenal ulcer medically here, as one does not have any measure of intelligent cooperation on the part of the patients, and as it is impossible for them to obtain anything approaching an ulcer diet in their homes.

During the two years that I have been in Abyssinia, approximately 200 patients with acute and chronic gastric and duodenal ulcers have presented themselves at the clinic of the American Mission Hospital, Addis Ababa, Abyssinia. Of this number several were first accepted for gastric study and medical treatment, but later this proved worthless. Thereafter all patients who for several years had suffered with vomiting and pain and who gave evidence of pyloric obstruction were admitted to the hospital if consent was obtained to an operation if necessary, patients with the more acute condition, without pyloric obstruction, were given medicine and dietary directions in the outpatient department, and an attempt was made to control them outside the hospital.

In the last two years, sixteen of the many patients with gastric disturbance for many years (ranging anywhere from four to fifteen years of vomiting, hematemesis, melena and epigastric pain) consented to operation. In all instances hyperacidity ranging from 70 to 120 cc of tenth-normal sodium hydroxide and great pyloric obstruction were found, in most cases almost all of the test meal was returned after seven hours, and in some cases the remains of beans, native bread and other native food eaten as early as forty-eight hours before admission to the hospital were found in the stomach washings. All the patients except

one were men, owing perhaps not to the greater preponderance of the disease among men, but to the fact that it is difficult to get the consent of the husbands for women to come to the hospital for operation. The ages ranged from 17 to 55 years. In all the patients except the 17 year old boy mentioned there were multiple healed ulcers, and occasionally an ulcer in the acute or chronic stage, the pyloric region was converted into a hard, scarred fibrotic ring with the lumen greatly constricted. In many cases the healed ulcers were on both the anterior and the posterior aspects of the pyloric portion of the stomach, and the stomach was adherent to posterior structures at several points, which proved to be scars of old ulcers. In all these cases posterior jejunostomy was performed. The patient, aged 17, had had symptoms of gastric ulcer for only six months, but he showed a great return of the test meal after seven hours. As the patient was the servant of a government official, a fluoroscopic and roentgenologic study of the gastro-intestinal tract was made at the small hospital of His Majesty, the King of Abyssinia. This disclosed a definite niche just proximal to the pylorus on the lesser curvature. The roentgenogram did not account for the failure of food to move on quickly, the barium meal seemed to move out of the pylorus into the duodenum normally. Operation disclosed an ulcer of the stomach exactly as seen in roentgenograms, the pylorus was entirely normal, but in the first inch of the jejunum there was a large chronic jejunal ulcer which had scarred down to such an extent that the lumen of the jejunum was almost obliterated. An adequate posterior gastrojejunostomy was performed just distal to the constricted portion of the jejunum. The patient had no more complaints, and the gastric ulcer healed spontaneously.

The director of the Negus Tafari Hospital of His Majesty the King, at Addis Ababa, informed me that his opinion on the relative frequency of gastric and duodenal ulcers among the black people in Abyssinia coincided with mine. At this hospital roentgen diagnosis is made, but not in all cases, as most of the patients are indigent and as the cost of x-ray materials is excessive. In most cases in which the roentgen rays have been used in the study of ulcer, however, gastric ulcers and pyloric obstruction were demonstrated by roentgenograms and by fluoroscopy. This hospital has averaged eight posterior gastroenterostomies for chronic gastric and duodenal ulcer per year in the last three years, all in black persons. It is peculiar that with 5,000 white inhabitants in Addis Ababa, not one white person with gastric or duodenal ulcer has come to the two hospitals. Hence, I would be forced to conclude from these statistics that gastric and duodenal ulcer is common among the black people, but rare among the white people. Conversely, since the white population furnishes the cases for appendectomy, I would conclude that acute appendicitis is rare among the black

place in general, but common in the white race. The latter statement conforms with general surgical opinion.²

When one seeks factors among the Abyssinians that differentiate them from the Negroes of America, one finds the most striking difference in the diet. Lesser factors, such as the fact that approximately 95 per cent of the population is constantly the host of the beef tapeworm, the greater frequency of other helminthic parasites, especially *Ascaris lumbricoides*, and the greater frequency of syphilis (from 90 to 95 per cent of the population is infected), may be ruled out as helminths affect chiefly the lower part of the bowel and as syphilis rarely causes ulcers of the stomach. A high percentage of the Negroes of the United States have syphilis, hence one would expect gastric ulcer to be common among them if syphilis were a causative factor.

The striking thing concerning the Abyssinians is their diet. The chief articles of diet are a heavy sour bread and a sauce that is approximately 50 per cent cayenne pepper. The sour bread is in the form of an immense thin pancake, part of it is broken off, rolled up in the form of a cornucopia, plunged into the pepper sauce so that a few tablespoonfuls of the sauce fill the cone, taken into the mouth and, almost without mastication, washed down with copious draughts of honey-water. My first native meal of bread and pepper sauce caused numerous herpes blisters about the mouth, and I have since eaten it only occasionally and then diluted.

When one considers the action of this pepper as a constant diet, one is led to expect gastric derangements. A standard textbook on therapeutics states

Capsicum, U.S.P. (Cayenne Pepper, African pepper). Externally applied, capsicum excites burning and redness, and in concentrated form even vesication. When taken internally in small doses, it produces a sense of warmth in the stomach, stimulates peristalsis and aids in the expulsion of flatus. Large doses produce severe irritation of the gastro-intestinal tract, characterized by pain, vomiting, purging and dysuria, with scanty dark-colored urine. It is employed chiefly as a rubefacient, stomachic and carminative.⁵

When one considers that from the time native babes are weaned approximately at the age of 2 years, until old age, the diet contains monotonously the same dishes of sour bread, pepper sauce, mildly intoxicating drinks and occasional beans, peas and slightly cooked or raw meat, it is not surprising to find disturbances of the stomach a common occurrence and, at an early age, a contracted and scarred pylorus. It would be interesting to compare the incidence of gastric ulcer in other countries having a very high pepper diet with that of Abyssinia.

5 Stevens. A Text-Book of Therapeutics, ed 6, Philadelphia, W. B. Saunders Company, 1923, pp. 202 and 203.

In considering any theory of the pathogenesis of gastric ulcer in Abyssinia, one is forced to lean strongly toward the theory that these ulcers are caused by a chemical action on the mucosal cells. Hence one would support the so-called digestive or corrosive theory of the pathogenesis of gastric ulcers. The chronicity of the ulcers is, no doubt, due to the continuation of the chemical insults to the gastric mucosa. This would be in harmony with Ivy's⁶ views that the chronicity of the ulcer is due to a general lowered resistance of the body and a period of temporary hypo-acidity or achylia. A gastric mucosa that is frequently damaged by extremely irritating food would respond immediately by hypersecretion of gastric juice with increased acidity, but immediately following such periods of gastric inflammation and hyperacidity there would be a shorter or longer period in which the gastric mucosa was readjusting itself, and diminished acidity would result. Many of these patients with chronic gastric and duodenal ulcers are in a state of general lowered resistance to all infection owing to malnutrition and occasionally to tropical diseases, such as frequent attacks of malaria, relapsing fever, typhus and the dysenteries.

CONCLUSIONS

The black people of Abyssinia represent an exception to the general rule that gastric and duodenal ulcers are rare in the black race. There is perhaps nothing in the black race per se that makes gastric ulcer uncommon in the Negroes of the United States. The chief factor in the production of gastric ulcer among the Abyssinians is an unusually high red pepper content of the diet.

⁶ Ivy, A. C. Contributions to the Physiology of the Stomach, *Arch. Int. Med.* 25:11 (Jan.) 1900.

GASTRO-INTESTINAL MYIASIS

REPORT OF A CASE

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Infestation of various parts of the human body by dipterous larvae was probably recognized by the ancients as early as the time of Homer, who wrote of a man affected by maggots. The first authentic case of myiasis, however, seems to have been reported by Leeuwenhoek about the seventeenth century when he described an infected wound of the leg caused by fly larvae.

The literature contains numerous reports of infestations of the ear and nose and of external wounds, but those of the gastro-intestinal tract are comparatively rare, there being but sixty-three cases reported to date. Of these, twelve were caused by *Fannia canicularis* or the black flower fly, eleven by *Musca domestica* or the common house fly, four by *Fannia scalaris*, six by *Sarcophaga* or the flesh fly, three by *Prophila casei* or the cheese maggot fly, twelve by *Eristalis tenax* or the drone fly, one by *Calliphora erythrocephala* or the so-called bluebottle fly, one by *Anthomyia radicum* or the root maggot fly, and one by *Muscina stabulans* or the stable fly, five cases were unclassified, in six cases there was a combination of two different infesting flies, and in one case there were three different types.

The case that I shall present is one of gastro-intestinal myiasis caused by *Musca domestica* and *Stomoxys stabulans*. This is the first case in the literature, I believe, in which both flies were found, and it is but the second time the stable fly has been mentioned as the infesting agent. The first case was reported by Portschnsky in 1913, and occurred in a Russian peasant. This is also the first time that pupa cases have been reported as being found in the stools.

REPORT OF A CASE

History—The patient was a white boy, aged 15 months, whom I delivered at the hospital. Labor was uneventful, being a left occipito-anterior presentation and not prolonged. The infant, however, had an elevated temperature for ten days, and on three occasions vomited a small amount of fresh blood. On discharge from the hospital he seemed to be normal. The following five weeks were spent

in a distant city. Then the child was readmitted to the hospital suffering from marasmus. He weighed only 5 pounds 2½ ounces (2.3 Kg) as compared with a birth weight of 6 pounds 14 ounces (3 Kg). On discharge, three weeks later, he had gained to 6 pounds 10 ounces (3 Kg). After three weeks' stay at home he was again returned to the hospital, this time as a boarder. He remained for two weeks, and was discharged weighing exactly 7 pounds (3.2 Kg).

The child was not seen again for thirteen months. Then the mother brought him into the office complaining that for a little over a year he had been having convulsions. They recurred daily and varied from two to seven seizures in twenty-four hours. His appetite was extremely poor, the bowels moved once a day, and he urinated normally. He was unable to sit or even to hold the head erect. His diet was composed of a dried milk preparation, full strength, orange juice, cooked cereal and cod liver oil. Increase of the total intake or the addition of solid food seemed to cause a greater number of convulsions. One year previously he had passed many thread-worms which were identified as such by a physician.

Examination—Physical examination revealed a pale child aged 15 months, with a somewhat imbecilic expression, uninterested in his surroundings. He could neither sit nor hold the head erect. The legs would not support the weight of the body. He weighed 19 pounds (8.6 Kg). Only three teeth had erupted instead of the usual twelve to sixteen normally found at this age. A rachitic rosary was present. The urine was normal. The blood count showed hemoglobin, 85 per cent, red blood cells, 4,850,000, white blood cells, 7,900, polymorphonuclears, 31 per cent, lymphocytes, 68 per cent, basophils, 1 per cent, the erythrocytes were normal in size and shape. Gastric analysis was made, fasting content free hydrochloric acid, 12, combined acidity, 58 and total acidity, 70, one-half hour test meal free hydrochloric acid, 11, combined acidity, 14, and total acidity, 25, one hour test meal free hydrochloric acid, 13, combined acidity, 12, and total acidity, 25. The examination otherwise gave essentially negative results. During the examination a convulsion occurred beginning with a tremor of the right side of the face, then extending to the right arm and leg and finally spreading to the whole of the body. It lasted for several minutes.

Course—After a five weeks' treatment consisting of two ultraviolet irradiations per week and an increased diet of various fresh vegetables, the convulsions decreased to one about every four days. They were much milder. It was at this time that the mother stated that the child was passing some "white worms" in the stools. She was instructed to bring the diaper immediately if this occurred again.

During the sixth week she came to the office with a fresh stool as directed. The diaper was found to be alive with maggots which were mixed throughout the stool. They were a dirty gray, about 1 cm in length, and propelled themselves like caterpillars. They were composed of about twelve segments with a black dot at the anterior pointed extremity.

On further examination of the stool numerous brown pupa cases were found, which were about one-fourth inch (0.6 cm) in length. At this time neither the larvae nor the cases could be identified. Eight of the pupa cases, however, were placed in a tightly covered glass jar and kept at room temperature. Several days later the cases were found open, and the adult flies flying about in the container. These together with the larvae and empty pupa cases were taken to Prof. Norman Phillips of the Zoology Department of Syracuse University, who identified the larvae as those of *Musca domestica* and the adult flies as *Stomoxys stabulans*.

This identification was later confirmed by Prof O A Johannsen of the New York State College of Agriculture at Cornell University. A peculiar thing was that all of the larvae were of the *Musca domestica* species, while all of the adult flies were of the *Stomoxys stabulans* type.

The mother stated that a week previously she had found several similar maggots on a diaper which contained no fecal matter, but had merely been soiled by urine. She said that the diaper had been perfectly clean when it was put on, having been boiled and laundered that same day.

Three weeks after the discovery of the first larvae, the child became restless and cried a great deal, whereupon the mother gave him a large dose of castor oil. The next day there were again maggots present in the stool in great numbers. This time they were smaller. These, unluckily, were not sent in for identification.

Nine weeks later larvae were found in the curds of milk vomited by the child. These, also, were smaller than the first. During the following week a portion of fecal matter which contained no larvae or pupa cases on examination was placed in a covered, sterilized container, and twenty-four hours later was found to contain numerous very small maggots.

Shortly after this, on October 12, the family moved into another home. Strangely enough, no more larvae or ova were ever again demonstrated in the stools, although a thorough search was made for six weeks. Whether the new home surroundings or the time of year influenced this, I cannot say.

Three months later the child's convulsions had entirely subsided, none having occurred for over ten weeks. He could hold the head erect and sit with little help. He looked and acted more like a normal child. The appetite was better, and he had ten teeth. His weight was 30 pounds (13.6 Kg).

Outside of the ultraviolet rays and dietetic measures, the only treatment that he received was an enema of double strength saline solution morning and evening for about three weeks. No drugs were given by mouth.

COMMENT

The mode of infestation in cases of gastro-intestinal myiasis is still a matter of hypothesis. There are several ways in which a person might become infested: (1) The ova might be ingested in the food, (2) the larvae might be ingested in the food, (3) a fly attracted by the food on the lips might lay the eggs here, and the patient might carry them into the stomach in this way, (4) cases have been reported in which the fly has deposited the eggs around the anal or urinary orifice and on hatching, the larvae have migrated into the rectum or the urethra.

In the case reported here the first suggestion is probably the correct one, for it has been seen that a portion of fecal matter containing no larvae on passage contained many very small maggots after being kept for twenty-four hours. This indicates that the ova must have been in the stool. Furthermore, the great number of larvae found at one time makes it unlikely that this quantity could have been taken without being noticed. The fact that the child vomited small larvae indicates that the ova were probably taken by mouth and hatched in the stomach and not

acquired through the rectum. The lowered resistance of the child, together with the low acid content of the stomach, probably accounts for the nondestruction of the ova by the gastric juices.

Chatin's experiments with larvae taken from one of his cases shows that they not only lived for several days completely immersed in oil or water, but also survived when introduced into the stomachs of various mammals. He also proved their power of resistance to gastric juice and their small need of oxygen.

LIFE HISTORY

*Musca Domestica*¹

Adult lays from 75 to 150 eggs at intervals of from 3 to 4 days in from 2 to 4 layings

Eggs hatch in from 12 to 24 hours

Larva stage lasts from 4 to 6 days

Puparium lasts from 5 to 7 days

From egg to adult in from 10 to 14 days

Adult lives from 30 to 60 days

May hibernate in the winter

Usually lays eggs in excrement, especially in manure heaps

Larvae lives best in manure but may exist in decaying fruits, moist bread or cereals

Larva is strongly, negatively helio-tropic

Females begin to deposit eggs from 9 to 12 days after emerging from the pupa case

*Stomoxys Stabulans*²

Adult lays from a few to 122 eggs in clumps of from 3 to 25 in 3 or more layings, greatest number during life is 632

Eggs hatch in from 1 to 3 days

Larva stage lasts from 11 to 30 days

Puparium lasts from 6 to 20 days

From egg to adult in from 14 to 25 days

Adult lives from 2 to 29 days

Usually pass the winter in the larva state

Usually lays eggs in straw or manure heaps

Larva is susceptible to heat or dryness

Larva is destroyed by bright light

Pupa are resistant to heat and drying

The life histories of the two species found is of interest because by comparison it is certain that the ova must have been ingested at different times, otherwise the pupa cases of *Stomoxys stabulans* would not have been found at the same time as the larvae of *Musca domestica*. Reference to the comparative table of life histories of these two flies shows that it takes from twelve to twenty-four hours to hatch the ovum of a house fly, and that it stays in the larval state for from four to six days, while the stable fly requires from one to three days to hatch and remains a larva for from eleven to thirty days before pupation.

1 Hewitt, C. Gordon. The House-Fly, London, Cambridge University Press, 1914, pp. 301-308.

2 Bishop, F. C. The Stable Fly, Farmers Bull. 1097, Washington, Dept. of Agriculture, U. S. Printing Office.

Authorities differ as to the symptoms and severity of gastro-intestinal myiasis. Osler said that the larvae may cause no symptoms or may cause serious intestinal ulceration manifesting itself by a dysenteric disease, with at times a fatal result. Anders simply stated that the condition may occur. Eugene Whitmore³ said that nausea, vomiting

A List of the Case Reports of the Internal Infestation of Man by Diptera

<i>Fannia canicularis</i>		<i>Fannia scalaris</i>	
Tulpus	1672	Laboulbens	1856
Stephens	1905	Judd	1876
Cattle	1906	Austin	1901
Blankmeyer	1907	Riley and Johannsen	
Hewitt	1909		
Chevril	1909		
Garrod	1910		
Solan	1910		
Blankmeyer	1914		
Franchini	1924		
Hart	1912		
Theobald	1901		
<i>Sarcophaga</i>		<i>Eristalis tenax</i>	
Higgins	1890	Odhelius	1789
D. Kellin	1925	Wagner	1870
Blair (2 cases)	1927	Leidy	1874
Cairns	1906	Riley	1890
Wohl	1913	Riley and Howard	1890
		Shettuck	1908
		Hall and Muir	1913
		R. Taggioli	1927
		Files of U. S. Bureau of Entomology (4 cases)	1905, 1905, 1906, 1910
<i>Phlebotomus</i>		<i>Musca domestica</i>	
Theobald	1901	Portschinsky	1913
Paris	1913		
Austin			
<i>Calliphora erythrocephala</i>		<i>Fannia canicularis</i> and <i>Musca domestica</i>	
Austin	1905	Austin	
		Cockayne	1912
<i>Anthomyia radicum</i>		<i>Fannia canicularis</i> and <i>Musca corvina</i>	
Austin		Stephens	1905
<i>Fannia scalaris</i> and <i>Fannia canicularis</i>		<i>Anthomyia</i> and <i>Sarcophaga</i>	
Jennings	1839	F. C. Wellman	
Czokov			
<i>Musca domestica</i>		<i>Anthomyia canicularis</i> , <i>Musca domestica</i> and <i>Eristalis tenax</i>	
Lubinski	1885		
Cohan	1898		
Wirsung (2 cases)	1906		
Hewitt	1909		
Nicholson (3 cases)	1910		
Felt	1913		
W. M. Jones	1913		
John Rennie	1927		
		Unclassified Types	
		Chichester	1816
		Hope (3 cases)	1840
		Robineau Desvoidy	1849

and pain may be present if the larvae are in the stomach, while colicky pain and hemorrhage may ensue if infestation is intestinal.

In a study of the symptoms of sixty-three cases found in the literature, I found that vomiting was present in twelve, nausea only in five, constipation in three, diarrhea in eleven, bloody stools in seven, abdominal pain in twenty-one, anemia in six, headache in four, restlessness in five, convulsions in one, loss of sleep in two, vertigo in two, loss

³ Whitmore, Eugene, in Tice Practice of Medicine, Hagerstown, Md., W. F. Prior, Inc., 1924.

of weight in seven, dry cough in one and no symptoms in four. The species of fly did not seem to influence either the severity or the kind of symptoms.

Several treatments have been suggested by as many different physicians. Those most popular seem to be the use of santonin, pepo, oil of chenopodium or thymol.

While the literature contains only a comparatively few case reports of internal infestation of man by dipterous insects, it is probable that this condition is more common than is generally supposed.

A list of all the cases found, including the author, year reported and the infesting agent, is given in the accompanying table.

PRIMARY *BACILLUS PYOCYANEUS* MENINGITIS

REPORT OF A CASE WITH RECOVERY ~

WARREN T VAUGHAN, M D

REGINA BECK, M D

AND

TURNER S SHELTON, M D

RICHMOND, VA

Primary systemic *Bacillus pyocyaneus* infection is infrequent enough to merit discussion. This organism is usually considered as being of low pathogenicity, manifesting its presence occasionally as a secondary invader in localized pyogenic processes. Indeed, it has been found as an apparently nonpathogenic cutaneous parasite, showing some predilection for warm, moist, flexor surfaces. It is found as a secondary invader in such conditions as furuncles, infected wounds and septic pneumonia. It was formerly thought that even in these local infections *B. pyocyaneus* occurred only as a nonpathogenic parasite.

Kossel¹ collected a few cases from the literature, all in children in whom a fatal illness was found to be due to an infection of the blood stream with this organism. In another review of the literature, Rolly² collected a series of cases of infections of internal organs in which *Bacillus pyocyaneus* was either the sole or an associate invader. In this list were such diseases as perityphlitis, pyelonephritis, fistula, mastitis, prepatellar bursitis and panophthalmitis. Involvement of deeper tissues was represented by abscess of the liver, endocarditis and a case of meningitis in a child, reported by Kossel. He added to the list a fatal case of his own, in which *B. pyocyaneus* septicemia with meningitis developed in a woman after an incomplete abortion. The organism was isolated ante mortem from both the blood and the spinal fluid.

In a study of 12,000 autopsies, Fraenkel³ concluded that *B. pyocyaneus* was the primary invader in only 13 cases. In 1917, he presented a study of 26 cases of primary *pyocyaneus* invasion in which there were 21 children under 2 years of age and 5 adults. He observed cases of otitis, enteritis, ecthyma gangraenosum, endocarditis, sepsis and others, due directly to infection with this organism. He

~ Submitted for publication, June 23, 1930

1 Kossel. Ztschr f Hyg u Infektionskr **16** 368, 1894

2 Rolly. Munchen med Wchnschr **29** 1399, 1906

3 Fraenkel, E. Virchows Arch f path Anat **183** 405, 1906, Ztschr f Hyg u Infektionskr **84** 369, 1917

concluded that it may act not only locally and with the production of toxin, but also through the actual invasion of the internal organs. He expressed the belief that although this germ is rarely the primary cause of disease, nevertheless, the majority of such infections are acute, and fatal almost without exception.

Khewer and Koch⁴ described the usual clinical picture of general *pyocyaneus* infection as being accompanied by dyspnea, cough, diarrhea, hemorrhagic spots in the skin and splenic enlargement. Certain clinical symptoms have been mentioned as being characteristic of *pyocyaneus* septicemia, notably nausea, vomiting and diarrhea, pronounced dyspnea, a hemorrhagic eruption and splenic enlargement. Rolly found that while these symptoms are often present and suggest the possibility of *pyocyaneus* infection, these and other pathologic changes differ in no way from those found in septicemia and sepsis due to other bacteria, and he concluded that diagnosis can be made only on the basis of a positive *pyocyaneus* culture.

The organism appears to have a predilection for the lymphatic tissues. Fraenkel described several cases, especially in children, in which the portal of entry appears to have been the oral mucous membrane or the lymphatic system, especially the Peyer's patches. In the mouth and the intestine, the local infection may progress to the stage of necrosis.

PYOCYANEUS MENINGITIS

B. pyocyaneus infection of the meninges is undoubtedly rare. Neal⁵ stated that she had seen one case of meningitis due to this organism. Price's⁶ British textbook did not mention *B. pyocyaneus* as a possible cause of suppurative meningitis. Christian's "Oxford Medicine"⁷ made no mention of the disease. Cecil's⁸ American textbook mentioned its occurrence.

Of those few cases of *pyocyaneus* meningitis reported, the majority have been consequent on a recognizable case such as trauma or lumbar puncture, or they have occurred in association with a generalized infection. The case described by Rolly, previously referred to, accompanied a general septicemia.

4 Khewer, H. and Koch. *Pyocyaneus Meningitis*, Munchen med Wchnschr 71 867 (June 27) 1924.

5 Neal, in Tice, Frederick. *Practice of Medicine*, Hagerstown, Md., W. F. Prior Company, Inc., 1924, vol. 10, p. 255.

6 Price, Frederick W. *A Textbook of the Practice of Medicine*, New York, Oxford University Press, 1929.

7 Christian, Henry A. *Oxford Medicine*, New York, Oxford University Press, 1927.

8 Cecil, Russell L., and Kennedy, Foster. *A Textbook of Medicine*, Philadelphia W. B. Saunders Company, 1927.

That case described by Gaucherand and Pigeaud⁹ left one in doubt as to whether they were dealing with a case of pure meningitis or a concomitant infection of the blood stream. At delivery, the mother was found to be suffering from septic endometritis. On the fourth day signs of meningitis developed in the infant. After three weeks a pronounced hydrocephalus had developed, and *Bacillus pyocyaneus* was isolated from ventricular puncture. Apparently only the brain was examined at autopsy on the thirty-seventh day. Chiari¹⁰ discussed the occurrence of *pyocyaneus* meningitis and pericarditis in infants. In Abt's pediatrics, Cooke described *pyocyaneus* septicemia in the newborn, stating that there may be associated meningitis, but he did not mention the possibility of a primary *pyocyaneus* meningitis without septicemia.

Trauma may be the means of implantation. The case of Abadie and Laroche¹¹ followed an injury to the skull. The patient recovered. The case described by Palazzo and Ottolenghi¹² followed a gunshot wound of the dorsal part of the spine. In this case the patient also recovered after four months' illness. He was treated with an autogenous vaccine. Abadie and Laroche's patient was treated with intraspinal injections of 3 cc of his own blood serum.

Lumbar puncture appears to have been responsible for a number of cases. That of Sonnenschein,¹³ followed by a few hours a diagnostic lumbar puncture. At autopsy, abscess of the brain or any other possible antecedent etiologic factor was not found. Levy and Cohen's¹⁴ case occurred in a syphilitic patient following a diagnostic lumbar puncture. The patient recovered after five months.

Chauffard and Laroche¹⁵ reported a case of *pyocaneus* meningitis developing in a person who had been receiving intraspinal tetanus antitoxin. The blood remained sterile and the patient recovered.

9 Gaucherand and Pigeaud. Meningitis from *Bacillus Pyocyaneus* in a New-Born Child. Fatal Case, Bull Soc d'obst et de gynec **17** 74, 1928.

10 Chiari, H. Bacterium *Pyocyaneus* Infection Producing Meningitis and Pericarditis in Infants, Centralbl f allg Path u path Anat **38** 483 (Oct 15) 1926.

11 Abadie, J, and Laroche, G. *Pyocaneus* Meningitis, Bull Acad de med, Paris **80** 15 (July 2) 1918.

12 Palazzo, R, and Ottolenghi, C E. *Pyocyanic* Meningitis, Rev sud-am de endocrinol **11** 616 (Sept 15) 1928.

13 Sonnenschein, C. *Pyocyaneus* Meningitis, Klin Wchnschr **2** 1758 (Sept 17) 1923, Fatal Meningitis After Lumbar Puncture, Deutsche med Wchnschr **49** 881 (July 6) 1923, abstr in J A M A **81** 1324 (Oct 13) 1923.

14 Levy, I I, and Cohen, A E. *Pyocyaneus* Meningitis After Lumbar Puncture, J A M A **85** 1968 (Dec 19) 1925.

15 Chauffard, A, and Laroche, G. A Case of *Pyocvaneus* Meningitis, Bull et mém Soc méd d hôp de Paris **41** 646, 1917.

In Schlagenhauser's¹⁶ five cases the meningitis developed following lumbar anesthesia. Sonnenschein collected eight such cases from the literature.

PRIMARY PYOCYANEUS MENINGITIS

Kliewe and Koch⁴ described a case of meningitis in a child aged 3 years that appears to have been a spontaneous infection without antecedent trauma or lumbar puncture, the only probable source being a preexisting aphthous stomatitis. The classic symptoms, with opisthotonos, positive Kernig sign, stiff neck and symptoms of irritation of the pyramidal tract developed. The spinal fluid pressure was increased, the cell count was 200 per cubic millimeter, and *B. pyocyaneus* was recovered from the spinal fluid. The child recovered gradually after having fever for eighty days. At discharge, the spinal fluid still showed a slight increase in albumin, a cell count of 32 and a sterile culture.

Summarizing the available literature, one may conclude that *B. pyocyaneus* meningitis is rare, and that when it does occur it is usually secondary to a blood stream infection or to direct implantation following trauma or lumbar puncture. There has been at least one case in which primary meningitis appears to have followed local infection in the mouth.

REPORT OF CASE

Miss A. R., aged 40, dated the onset of her symptoms from the middle of May, 1928. The onset followed a mild cold in the head, and the symptoms consisted of frontal headache, followed later by severe pains in the neck, the region of the right elbow and the fleshy part of the right hip. These various pains, at times severe enough to require morphine for relief, were intermittent and there were periods when she was entirely free from discomfort. When the patient was first seen on May 26, the temperature was normal.

A detailed examination on May 26 gave essentially negative results. From this date to July 9, at which time she was admitted to the hospital for diagnostic lumbar puncture, the symptoms gradually became more severe, but throughout the month of June she remained up and about most of the time. Her temperature did not exceed 99.6 F.

Rhinologic consultation on June 22 revealed no evidence of sinus disease and no pathologic condition other than chronic tonsillitis and mild chronic hypertrophic rhinitis. Detailed physical and neurologic examinations on July 5 again gave negative results. The laboratory studies, including a hemocytologic examination, a Wassermann test of the blood, chemical analysis of the urine and determinations of nonprotein nitrogen and sugar in the blood were likewise negative. Roentgen examination of the sinuses and sella turcica on July 9 gave negative results.

Diagnostic lumbar puncture on July 9 revealed a cloudy spinal fluid under distinctly increased pressure with a cell count of 1,882, of which 83 per cent were polymorphonuclears and 17 per cent were lymphocytes. The Noguchi globulin reaction was strongly positive. A gram-negative motile bacillus grew on culture.

Directly following lumbar puncture, the patient's temperature rose. By the next day, July 10, she presented the characteristic symptoms of meningitis with stiff neck, positive Kernig sign and a slight external squint of the left eye.

A second lumbar puncture on July 11 revealed a cell count of 3,800, and the same gram-negative motile bacillus was isolated. Both the blood culture, started on the same day, and the Vidal test were negative.

On July 12 ventriculography was performed in a search for possible abscess of the brain. The results were negative. However, immediately following this operation the patient began to improve, and the temperature began to fall. No new neurologic signs became manifest throughout the remainder of her illness. Three days after operation, lumbar puncture showed a clear fluid with about 100 cells per cubic millimeter. The patient was discharged from the hospital on July 21, nine days after the operation. At that time the temperature was normal, but she was still slightly irrational. The latter symptom cleared up a few days after her return home. She had remained well when last observed (June, 1930).

A specimen of spinal fluid obtained July 16 agglutinated the autogenous *B. pyocyaneus* in a dilution of 1:60. The blood serum did not agglutinate the organism.

A diagnosis of basilar meningitis due to *B. pyocyaneus* infection was made.

Early in the patient's convalescence a nasopharyngeal swab was obtained. *B. pyocyaneus* did not appear in the culture from this swab.

The following laboratory studies were made on the specimen of the spinal fluid obtained July 10. The fluid was cloudy in appearance. The cells numbered 3,200. 75 per cent were polymorphonuclears and 25 per cent lymphocytes. The globulin reaction was 4 plus, and the colloidal gold curve, 0000011100. The Kahn test gave a reaction of 2 plus, the Kolmer test was slightly anticomplementary, and there was 21 mg of sugar per hundred cubic centimeters. Direct smear showed many gram-negative bacilli, morphologically resembling typhoid bacilli except that some were somewhat greater in length. A hanging drop preparation made from the spinal fluid showed a very motile bacillus. Culture mediums gave the following results: Rosenow's brain broth was cloudy and green after five days. Plain broth was turbid, with a thin scum, it was pale green after five days. Loeffler's medium became liquefied and brownish. On plain agar, a moist whitish growth was noted, the culture was a very pale green in the butt of the tube on the third day. Both Russell's double sugar and Kendall's double sugar mediums were negative for acid and gas. Litmus milk showed coagulation and no acid. This medium started to clear at the top on the second day. Digestion of milk was noted, the liquid was muddy yellow in five days. Saccharose was negative for acid and gas and pale green on the second day. Dextrose, lactose, maltose, mannite and levulose were all turbid and negative for acid and gas. No color was noted.

An emulsion of organisms was made from the broth culture. These organisms were agglutinated against the patient's serum. The result was negative. This same emulsion was agglutinated against a second specimen of spinal fluid collected on July 16, and agglutination was positive in dilution (1:60). A specimen of normal spinal fluid could not be secured for a control, but organisms did not agglutinate in the patient's serum or in the salt solution control.

On July 13, 1928, a culture of the blood was negative after six days' incubation.

A second specimen of spinal fluid was collected on July 16. It was clear in appearance. The cell count was 102, 37 per cent were polymorphonuclears, and 63 per cent were lymphocytes. The globulin test gave a reaction of 4 plus, the colloidal gold curve was 1111234210 (a curve typical of meningitis). A culture

of the spinal fluid was negative Wassermann and Kahn tests made on a second specimen of spinal fluid were negative Wassermann and Kahn tests of the blood were negative

After standing at room temperature for five days the first specimen of spinal fluid was green

COMMENT

This case showed some points of similarity with that described by Sonnenschein In the latter, a robust man, aged 20 had had symptoms, especially headache and pain in the left leg for the preceding ten months, dating from an injury to the head He did not have fever A Wassermann test of the blood was negative A few hours after a lumbar puncture yielding clear spinal fluid, the characteristic symptoms of meningitis, with fever developed Four days later the spinal fluid showed an increased cell count, and from it *B. pyocyaneus* was cultivated The blood serum later agglutinated this organism in a dilution of 1:200 The patient died on the ninth day of his illness

At autopsy, a purulent spinal and basilar meningitis was observed Pus was also found in the third and fourth ventricles Abscess of the brain was not present The internal organs showed no changes other than a few patches of erosion in the small intestines *B. pyocyaneus* was cultivated from the ventricles, the meninges and the spleen

Aside from the clear first specimen of spinal fluid and the ultimate outcome, the cases are parallel Our own case appears to substantiate the common belief that *B. pyocyaneus* is an organism of low virulence Other cases of recovery previously cited give further confirmatory evidence It seems to us that even with a negative first specimen of spinal fluid, it is possible that the patient in Sonnenschein's case had been suffering from a low grade localized basilar meningitis of rather long duration that became disseminated following lumbar puncture This is merely suggested as an alternative explanation

Schneider¹⁷ described a case following spinal anesthesia in which the infection appears to have been primary in the meninges, but also to have spread to the blood stream, and in which recovery took place after eighty-four days of illness It is of interest that in his case also, the patient was often afebrile, with flares of temperature immediately succeeding the lumbar punctures He attributed recovery in his case to the intraspinal injection of a dyestuff and the intravenous injection of a silver preparation

The diversity of therapeutic measures apparently successful in cases in which the patient has recovered (dyes, autogenous vaccine, intra-spinal autoserotherapy, decompression and spinal drainage) lends color to the assumption that in these cases there is some natural tendency to recover

¹⁷ Schneider, Hans Zur Klinik und Therapie der pyocyanus Meningitis, Wien klin Wchnschr 37 65 (Jan 17) 1924

Nature has protected the central nervous system and its meningeal covering with the greatest care against invasions from without. The barriers are chiefly mechanical and are adequate enough for nearly all contingencies. Probably as a result the local immunity barriers are less abundant and less effective than in other tissues more exposed to external contact. As a consequence bacteria that under ordinary circumstances are of low pathogenicity or even usually without pathogenic action in man may prove to be highly infectious and even fatal in the event that they find their way to the meninges.

The relative frequency of recovery from meningitis due to this decidedly infrequent organism, recovery in tissues inadequately equipped immunologically, indicates that the low pathogenicity of *B. pyocyaneus* is due not so much to a high degree of immunity on the part of the tissues as to a low invasiveness on the part of the micro-organism.

CONCLUSIONS

From a study of the case herein reported and a review of the available literature, it becomes evident that the case presented is of especial interest because of the following factors: (1) primary *pyocyaneus* meningitis with minimal systemic and localizing symptoms and with no recognized portal of entry, presumably the infection entered through the lymphadenoid tissues of the upper part of the respiratory tract or through similar tissues of the digestive tract such as the Peyer's patches; (2) absence of the three recognizable etiologic factors found in other cases in the literature, namely, trauma to the brain or spine, lumbar puncture or *pyocyaneus* septicemia; (3) seemingly good therapeutic results from decompression; (4) evidence of the local character of the infection as seen in the development of agglutinins in the spinal fluid but not in the blood stream; (5) rapid recovery in contrast to the two other general types of cases heretofore described: (*a*) rapid, fatal progression, and (*b*) a long drawn out recrudescient illness; and (6) evidence that even in *B. pyocyaneus* meningitis one is dealing with an organism of relatively low invasiveness.

Book Reviews

DIE HYPERTONIEKRANKHEITEN By ESKIL KYLIN Second edition Price, 22 marks Pp 270, with 28 graphs Berlin Julius Springer, 1930

After four years of additional study Kylin offers a thoroughly revised and enlarged edition on hypertension adapted as a text for physicians Dealing as it does with a subject so basically controversial and in connection with which there is such a paucity of complete data, the book is refreshingly free from metaphoric aphorisms, rehash and startling therapeutics The bibliographic background, as well as his own research, is wide and authoritative

Kylin first investigates the normal values of the arterial and capillary pressure On consideration of an extensive critique of the clinical methods and statistics he establishes the normal systolic arterial pressure as from 100 to 145 mm of mercury under 40 years of age, and from 145 to 150 mm over that age Daily fluctuations are not in excess of 15 mm The normal capillary pressure is from 80 to 200 mm of water, with daily variations not exceeding 40 mm The values for capillary pressure are independent of age The normal anatomy and physiology, as well as the permeability and pathologic physiology of the capillaries, are detailed with erudition in relation to the maintenance of the blood pressure

The mechanism of hypertension is then studied The insignificance of the cardiac factor, blood volume and viscosity as well as sclerosis of the larger vessels, is proved Attention centers on the arterioles and capillaries Experimental and clinical evidence negates the origin of hypertension from renal, metabolic product retention, epinephrine or unknown pressor sources The modern conclusive concept, brilliantly supplemented and summarized by Kylin, identifies hypertension with changes in the capillaries and arterioles Renal changes are secondary throughout

Clinically, the hypertensive diseases exist in two groups essential hypertension and acute universal capillaropathy (so-called acute glomerulonephritis)

Essential hypertension is seen as a hereditary, constitutional, autonomic, vasomotor neurosis with hormonal disturbances Constitution, the vegetative system and the endocrine glands are inseparably involved in the abnormal reaction of the body The abnormal reaction is manifested in a multiplicity of phenomena Patients or their families tend to have diabetes, gout, adipose constitution, asthma, migraine, spastic colitis and vasomotor disturbances The onset often occurs at the menopause Raab's remarkable research determining a hypersensitivity of the vasomotor centers of hypertensive persons to the carbon dioxide content of the blood is cited The essential hypertensive patient inclines toward vagotonia The blood potassium is high, the calcium and the cholesterol, low The reaction to epinephrine is paradoxical An insulin depressor effect is more decided The compensatory hypoglycemia following a test on the sugar tolerance is more marked In addition, there is slight hyperglycemia, diminished sugar tolerance and a flattening of the epinephrine blood sugar curve The patients are intolerant to heat

In essential hypertension the capillaries are normal, as to both morphology and tension The arterial pressure is at its highest in this form of hypertension and is based on arteriolar spasm Extensive daily fluctuations up to 100 mm of mercury are characteristic and attest to the concept of a functional vasomotor disturbance Diffuse arteriolosclerosis, which is a concomitant pathologic change is similarly interpreted as an end-stage of arteriolar work-hypertrophy Of interest is the therapeutic benefit of atropine, calcium, extracts from the sex glands and injections of nonspecific protein

Acute universal capillaropathy is subdivided into the postinfectious type (so-called acute glomerulonephritis) and that of pregnancy, which are basically similar

Pathogenically, a toxin — on the one hand streptococcic, on the other presumably of placental origin — is held responsible. The toxin produces a universal capillary dilatation with an axon reflex contraction of the arterioles. The vessels of the kidney are merely more sensitive and hence more involved. Further injury is evidenced by morphologic changes in the capillaries. The primary site of action is the capillary, the arteriolar response is secondary.

The capillary pressure rises to from 300 to 400 mm of water with daily fluctuations up to 130 mm. The arterial pressure rises moderately and shows only insignificant daily variation. Edema is based on the increased permeability of the capillaries. This may be due to changes in the wall of the capillaries, increased hydrostatic pressure or diminished osmotic pressure of the blood. Changes in the eyegrounds constitute advanced organic vascular injuries. Kylin emphasizes the fact that the rise in capillary and arterial pressure, as well as edema, precedes the urinary symptoms. Renal changes are only secondary. As regards the output of water, the kidney in itself may not be involved as the tissues bind the water, thus, severe oliguria may suddenly be followed by a marked polyuria and relief from edema. The blood shows a low value for calcium and protein, and low osmotic pressure.

Lastly Kylin considers the permanent diseases of hypertension as end-stages, often being combination forms of essential hypertension and acute diffuse capillaropathy. They are the result of irreversible organic vascular changes.

It is a review that makes evident Kylin's broad grasp of the subject as well as his thorough knowledge of the literature. It is a distinct record of advance in understanding a group of clinical manifestations that are of ever increasing importance and Kylin's own contributions in the field play a distinct role in this understanding.

CANCER OF THE LUNG AND OTHER INTRATHORACIC TUMOURS. By MAURICE DAVIDSON. Price \$5.50. Pp 173. New York. William Wood & Company, 1930.

When Adler wrote his monograph on "Primary Malignant Growths of the Lungs and Bronchi" in 1912, cancer of the lung was looked on by most physicians as an interesting rarity almost as difficult of diagnosis as of treatment. Since that time the picture has changed in many respects, but most remarkably in regard to the frequency of primary, malignant pulmonary disease. Since 1918, the literature of the entire world has been flooded with articles on the subject, indicating a world wide increase in the frequency of this condition. Few authors are found to doubt that this increase is real and not one of the common false trails of medical statistics. Although admittedly the development of roentgenology has disclosed vastly more cases than were recognized ante mortem in earlier days, the routine autopsy observations throughout the world have shown that a vastly larger proportion of dead bodies examined during the past decade exhibited primary cancer of the lung than did the bodies examined in the same institutions in previous years. Hence this monograph by Davidson, of the Brompton Hospital for Consumption and Diseases of the Chest in London, is altogether timely.

Davidson discusses the statistical evidence, and is convinced of a genuine increase in frequency, but is unable to advance an explanation on the basis of the facts and theories so far advanced. He merely makes the judicious statement, "It seems reasonable to suppose that for an explanation of the increase in primary carcinoma of the respiratory tract we must look to some factor which since the period of the war has begun to operate in greater degree and which through the production of specific tissue irritation, may account for this hitherto unusual localization of malignant disease in such individuals as are especially susceptible." The discussion of pathologic anatomy and etiology is brief, but adequate for a book manifestly primarily of clinical interest. Mention is made of the fact that since the time of Adler's report pathologists have more generally learned that most of the spindle cell or "oat cell" tumors of the lungs and mediastinum are not sarcomas but carcinomas, and it is now believed that sarcoma of the lung is rare indeed. Symptomatology and diagnosis are discussed sanely, and a score of new

cases are briefly reported. The fact is mentioned, but not extensively discussed, that not infrequently primary tumors of the lungs make their clinical appearance as diseases of the central nervous system, because of cerebral metastases.

Roentgenologic aspects properly come in for a large part of the discussion of these conditions, in which the roentgen observation plays the major part in diagnosis, and the reviewer noted with interest this statement: "The use of x-rays, however, in the diagnosis of nontuberculous diseases of the lungs has not received such general recognition in this country as it has on the Continent, and especially in the United States. This is a matter for regret, since a great deal of the success of modern diagnosis is due to the radiologist, in whose work departmentalism has become as inevitable as in almost every other science."

Altogether this is a well balanced and timely, but not exhaustive or original, presentation of a topic of immediate interest.

THE EDWIN SMITH SURGICAL PAPYRUS. VOLUMES I AND II. By JAMES HENRY BREASTED. Price, 4 pounds, 10 shillings. London: Cambridge University Press, 1930.

The first volume contains general explanatory notes for physicians and other non-Egyptological readers, followed by a general and then a special introduction, and finally the translation with commentaries.

The second volume contains forty-six facsimile plates of the original papyrus and on the opposite page a line for line hieroglyphic transliteration. As one compares these two pages it is evident that illegible writing is not a modern acquisition.

This is the oldest surgical papyrus. While this copy was prepared about 1700 B. C., the original papyrus from which it was copied probably dates back to 2500 or 3000 B. C. The scribe copied only the first portion of the original roll. The author is unknown, but evidently was a surgeon of eminent learning and wide experience. Apparently, this papyrus was an account of his observation on injuries to the human body. He begins with the head and goes downward to the neck and chest. The last case recorded was injury of the spine, and this ends the incomplete papyrus.

The author of this roll was the first physician to examine the patient and record the observations in an orderly manner, giving the physical observations, diagnosis, prognosis and treatment. Take as an illustration case 44. Title: "Instructions on a break in the ribs of the breast." Examination: "If thou examinest a man having a break in the ribs of his breast over which a wound has been inflicted, and thou findest that the ribs of his breast crepitate under the finger, then I should say, 'One having a break in the ribs of his breast over which a wound has been inflicted is an ailment not to be treated'." In many cases there are interesting case notes made at subsequent examinations. In this manner he describes forty-eight injuries. The author makes extensive and interesting commentaries on the exact meaning as interpreted from the hieroglyphics.

Professor Breasted has given us a masterpiece which must have required much study and thought. The medical profession interested in the history of medicine owes him a debt of gratitude for making this papyrus available in such an attractive form.

UMSTURZ UND AUFBAU DER PRAKTISCHEN MEDIZIN. VOLUME II, PART 1. VOLUME III, PART 2. By SANITÄTSRAT DR. KUSCHEL, Augenarzt in Ludenscheid. Price, 7 marks. Pp. 258, with illustrations. Oldenburg: Schützesche Hofbuchdruckerei, 1929.

These two parts of the large work come mainly under the category of medical curiosities and special pleading. The author is a practicing ophthalmologist. The subtitle of the first pamphlet reads: "The Crowning (Entthronung) of Bacteriology Through the Biophysics of the Atmosphere. Meteorology as the Basis of Physical Therapy, Medicine in the Service of Aeronautics." The dependence of living

processes on the atmospheric pressure, the oxygen of the atmosphere and, in part, the temperature is now fairly well understood. To be sure, we do not yet know the mechanism of the poisonous effect of high oxygen tension, but the author appears to go far afield in his endeavor to correlate atmospheric changes with all types of disease processes.

The second pamphlet is largely one of special pleading for what appears to be a proprietary ding, and more than two thirds of the pamphlet is taken up with tables and cases illustrating the cure of diverse diseases by what is called "Vital-saline," A, B, C, D, etc. These are various inorganic salts, single or in combination, such as sodium chloride, potassium chloride, magnesium phosphate, etc. With these the author reports cures or improvement of such diverse diseases as muscle weakness, rickets, rheumatism, headache, atony of the heart, stomach and uterus, asthma, arteriosclerosis, ulcer of the stomach and nephritis.

Throughout both pamphlets the author maintains that the therapies here advocated represent a new system of a rational and natural therapy. *Verbum sat sapienti*.

MOTHER ALPHONSA ROSE HAWTHORNE LATHROP. By JAMES J. WALSH, M.D., PH.D., Litt.D. Cloth. Price, \$2.25. Pp. 273, with index. New York: The Macmillan Company, 1930.

In September 1894, Rose Hawthorne Lathrop, the younger daughter of Nathaniel Hawthorne whom the literary friends of her father used to call "the Rose of all the Hawthornes," rented a little flat of three rooms and a kitchen at 668 Water Street, on the lower East Side of New York. This was in the heart of a very poor neighborhood, and Mrs. Lathrop's idea in locating there was to help some of the destitute poor who were suffering from incurable cancer to bear the pains and trials through which they had to go before death came to relieve them. She took several patients with cancer to live in this little apartment with her, she received others at certain times during the day in her own room so as to dress their lesions, and she visited as many more in their homes as her time and strength would permit her to attend. This was the beginning of a work that occupied the next thirty-two years of her life, until her death in 1926, at the age of 75.

In 1893, with her husband George Parsons Lathrop, she had become a convert to the Catholic Church and was stimulated by her conversion to devote herself during the years that were left to her to some task that would give to human existence a meaning in terms of another world than this. At this time one of her dear friends died of cancer, and shortly thereafter her attention was called to the case of a poor seamstress who was discharged from a hospital to die of this dread malady. She made inquiries and found that cancer was a rather common disease and entailed much suffering, not only because of the pain and physical discomfort but because of lack of care, companionship or diversion of mind, particularly in the cases among the very poor.

She fortified herself for the work by a three months' period of voluntary training in the New York Cancer Hospital. Other voluntary workers were obtained, and the little group called themselves "The Servants of Relief for Incurable Cancer," which, through gradual transformation and after much sacrifice and hardship, became a religious order affiliated with the Third Order of Saint Dominic. The story of the growth and development of this remarkable work of courage and devotion is one of the most appealing episodes in American life.

PHYSIOLOGICAL CHEMISTRY. A TEXT-BOOK AND MANUAL FOR STUDENTS. By A. P. MATTHEWS, PH.D., Carnegie Professor of Biochemistry, the University of Cincinnati. Fifth edition. Price, \$7. Pp. 1233. New York: Williams Wood & Company.

The new edition of this well known text is in the main a reprinting with such additions and alterations as could be incorporated without enlarging the work. Among the more important changes or additions are the treatment of the

structures of the disaccharides and polysaccharides and nucleic acid, the recent advances in nerve and muscle metabolism and the biochemistry of hemoglobin, bilirubin, sterols, bile acids, allantoin, hormones and vitamins. The work retains all of the outstanding features so characteristic of the author's writings. His style, originality and versatility are as refreshing and as entertaining as ever. He continues to accomplish what he hoped to attain in his first edition, namely, "to raise in the minds of those who read it more questions than it answers."

STALKERS OF PESTILENCE By WADE W. OLIVER, M.D. With an Introduction by Theobald Smith, M.D., Ph.D. Price, \$3. Pp. 251, with illustrations. New York: Paul B. Hoeber, Inc., 1930.

While this book is in purport and by title a history of the development of understanding of infectious disease, it is in reality a well rounded, if very brief, history of medicine and the knowledge of all illness. The record runs from the fossil remains of the Paleozoic period to the B.C.G. inoculations of Calmette. All of the great names in the history of the science come in for some consideration. In spite of its brevity it is a highly stimulating account of the march of progress of what is essentially pathology. As might be expected, the period beginning with Pasteur is most intensively treated, and Oliver's account furnishes an excellent introduction to the research of the great group of the last third of the nineteenth century. The size of the book is convenient, and the printing and illustrations are good. A feature of especial value is a fairly extended bibliography.

PHYSIOLOGIE UND PATHOLOGIE DER VERDAUUNG SAUGLINGSALTER By DR. E. FREUDENBERG, Professor an der Universität, Marburg. Paper. Price, 14.80 marks. Pp. 201, with 40 illustrations. Berlin: Julius Springer, 1929.

This is a timely, reliable and useful monograph on the physiology and pathology of digestion in infants. The author endeavors to summarize and criticize both the experimental data and the clinical observations that have accumulated during the last two decades in this field, the conclusions being submitted as guides for the practicing pediatrician. The chapters include the motor and secretory functions and disturbances of the alimentary canal in infancy and the digestion of proteins, carbohydrates and fats, as well as the rôle of bacteria in the alimentary tract in pathologic conditions. Each chapter ends with the useful references to the more important literature. The monograph will be helpful to both the pediatrician and the laboratory worker.

THE CANDIRU By EUGENE W. GUDGER, Ph.D. With a Foreword by Aldred Scott Warthin, M.D. Price, \$1.50. Pp. 120, with illustrations. New York: Paul B. Hoeber, Inc., 1930.

This little book will furnish any one entertainment well worth its modest price. The author takes a fish story, that of a minute South American catfish (*Candiru*), which according to native tradition inhabits by preference the human urethra, and without any obvious bias makes out a good case for its truth.

BLOOD PRESSURE BEFORE AND AFTER OPERATION IN HYPERTHYROIDISM *

LEWIS M HURXTHAL, M D

BOSTON

The relationship between blood pressure and hyperthyroidism is significant if some views of the present day are true. It is common knowledge that there is an increased pulse pressure in hyperthyroidism. Statements have been made that if this were continued over a sufficient time, cardiovascular changes and permanent arterial hypertension might ensue. Furthermore, it is the belief of some writers that the nontoxic adenomatous goiter can lead to similar changes over a period of years. There has been no adequate survey, as far as I am aware, to show that either active hyperthyroidism or prolonged but slight over-activity of the thyroid in otherwise clinically nontoxic goiter leads to permanent cardiovascular degeneration, hypertension or cardiac enlargement.

In observing patients who have been operated on for toxic goiter, one frequently finds the blood pressure higher after operation than before, although the basal metabolic rate is normal and the patient is clinically free from thyrotoxic signs or symptoms. One might assume that the preexisting state of hyperthyroidism had been a causative factor in the development of the vascular hypertension. These observations have probably led others to assume, and in certain instances have led me to wonder, whether or not there is any relationship. This study, therefore, was undertaken to determine (1) the blood pressure before and after subtotal thyroidectomy, (2) the relationship between the metabolic rate, the type of goiter and the blood pressure, (3) a comparison between the blood pressure of patients with toxic goiter after operation and the blood pressure of nongoitrous persons.

MATERIAL USED

The ideal method of study in a problem of this kind is an analysis of a large group of consecutive cases. Complete follow-up data are difficult to obtain when patients are widely scattered over several states. While most of my patients return for examinations two or three times during the year following operation, less than one-fourth return regularly every three months during that time. I analyzed 458 cases of toxic goiter,

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* From the Medical Department of the Lahey Clinic

regardless of the type, the occurrence of postoperative myxedema or recurrent hyperthyroidism. I found, however, that selected cases had to be used for special purposes. This selection was made on the basis of completed data for the questions at hand. Only cases free from recurrent persistent hyperthyroidism or postoperative myxedema were included.

It seems hardly necessary to state that all cases diagnosed as hyperthyroidism were clinically thyrotoxic. Patients with hypertension and elevated basal metabolic rates who have no clinical evidence of thyroid toxicity are not considered as having hyperthyroidism, are not operated on and therefore are not included in this study.

OBSERVATIONS

Basal Metabolism Determination—Unless the circumstances did not permit, the first basal metabolic rate in these cases was determined on the morning following the patient's admission to the hospital. A second basal metabolic rate was determined about the sixth day afterward. Unless the patient was unusually toxic or had some other complication, no further observations of the basal metabolic rate were made before the operation. In case that it was necessary to perform the operation in two stages, only one metabolic rate was usually recorded before the second stage. Six days after operation was generally the time at which the postoperative metabolic test was made.

The patients were asked to return every three months during the first year and once a year thereafter for observation. It was insisted that they enter the hospital on the night before observation, nothing was given to them by mouth after 8:00 p. m. that night. Phenobarbital was occasionally prescribed for restlessness. In the morning the patients were taken in wheel chairs to the metabolism laboratory, and after a rest of ten or more minutes the test was made. Thus, the best possible circumstances were provided for the estimation of the basal metabolic rate.

Blood Pressures—A reading of the blood pressure was made when the patients were first examined either at the clinic or at the hospital. Readings of the basal blood pressure were made by trained technicians at the time of each metabolism test. Thus, all the readings of the blood pressure were made under ideal circumstances and under conditions that could not be improved.

BASAL BLOOD PRESSURE

Determinations of the blood pressure made under basal conditions are lower than those taken at other times.¹ A comparison of the basal

¹ Addis, T. Blood Pressure and Pulse Rate Levels, Arch. Int. Med. **29** 539 (April) 1922.

and clinical blood pressures distributed by decades is shown in tables 1 and 2. In my experience a basal systolic pressure of 140 mm of mercury is often found to be from 150 to 160 mm, under the usual clinical conditions. A basal systolic blood pressure of 150 mm of mercury, is therefore, in most instances, indicative of hypertension.

TABLE 1—*Comparison of Clinical and Basal Blood Pressure by Decades (116 Cases of Exophthalmic Goiter)*

Decade	Clinical Blood Pressure, Mm Hg	Basal Blood Pressure, Mm Hg	Difference in Systolic Pressure, Mm Hg
20 to 29	150/73	130/64	20/9
30 to 39	146/73	131/69	15/4
40 to 49	164/76	152/73	12/3
50 to 59	166/76	159/73	7/3
Average for all groups	155/76	132/70	
Average difference			23/6

TABLE 2—*Comparison of Clinical and Basal Blood Pressure by Decades in Cases of Nontoxic Goiter*

Decade	Clinical Blood Pressure, Mm Hg	Basal Blood Pressure, Mm Hg	Difference in Systolic Pressure, Mm Hg
20 to 29	126/78	113/64	13/14
30 to 39	133/84	117/70	16/14
40 to 49	150/90	131/77	19/13
50 to 59	151/90	141/83	10/7
60 to 69	155/86	142/80	13/6

TABLE 3—*Average Basal Blood Pressure Readings by Decades in Cases of Exophthalmic Goiter and Toxic Adenomatous Goiter Before Operation*

Decade	Exophthalmic Goiter (225 Cases)		Toxic Adenomatous Goiter (78 Cases)	
	Basal Blood Pressure, Mm Hg	Number of Cases	Basal Blood Pressure, Mm Hg	Number of Cases
20 to 29	123/62	50		
30 to 39	131/67	50	127/72	12
40 to 49	144/77	50	137/74	19
50 to 59	155/73	50	158/81	33
60 to 69	161/70	25	161/87	14
		225		78

AVERAGE BASAL BLOOD PRESSURE IN HYPERTHYROIDISM BEFORE OPERATION

In table 3 are shown the basal blood pressure readings in the series of 225 cases of exophthalmic goiter and 78 cases of adenomatous goiter with hyperthyroidism. The group of 225 cases of exophthalmic goiter consisted of the patients requiring one or two stage operations and were selected according to decades. The 78 cases of adenomatous

goiter requiring one or more operations could not be selected in this way as there was not enough material. As can be seen, there is a definite average rise of both systolic and diastolic pressures with increasing age.

AVERAGE BLOOD PRESSURE CORRELATED WITH BASAL METABOLIC RATE

The relationship between the average blood pressure by decades and the basal metabolic rate is shown in chart 1. While the pulse pressure and rate are indicative of the basal metabolic rate as shown by Read²

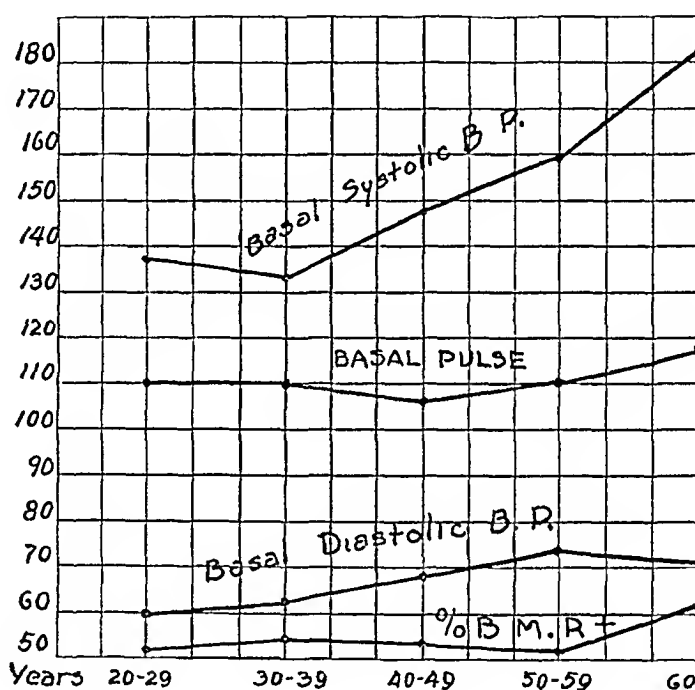


Chart 1—Correlation of the blood pressure, the pulse and the metabolism in the different age groups of 100 cases of exophthalmic goiter (two-stage operation)

in cases uncomplicated by cardiovascular disease, my studies show that this relationship does not hold for the general run of cases.

EFFECT OF SUBTOTAL THYROIDECTOMY

The data on 50 cases of exophthalmic goiter that were observed for a year are shown in chart 2. These cases were selected because the patients had returned at regular intervals of three months and all the data had been recorded. The result at the end of three months in 100 cases of exophthalmic goiter in which two-stage operations were deemed advisable is shown in chart 3. Chart 4 records the events in 38 cases of adeno-

² Read, J. M. Basal Pulse Rate and Pulse Pressure Changes Accompanying Variations in the Basal Metabolic Rate, *Arch Int Med* **34** 553 (Oct.) 1924

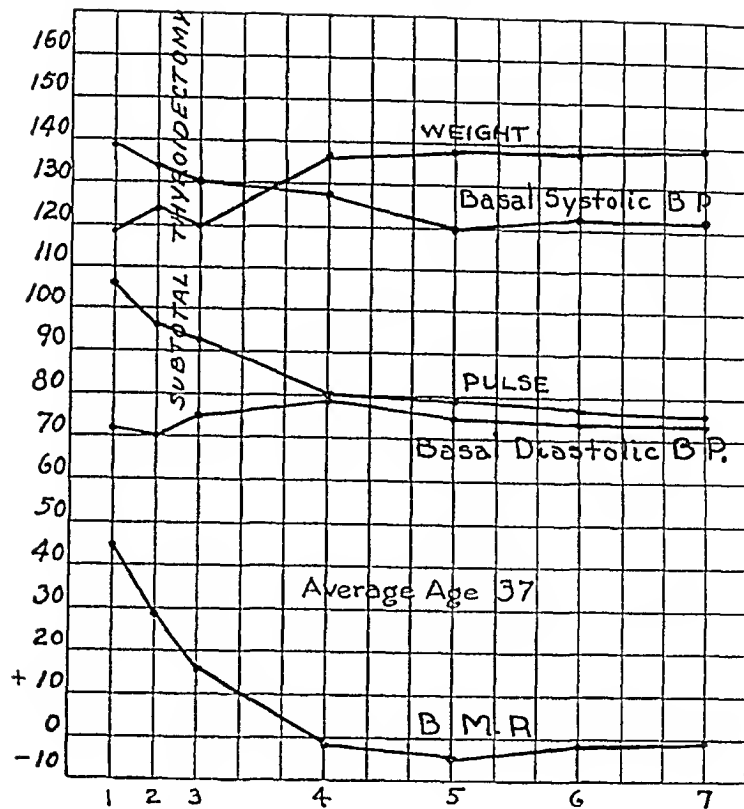


Chart 2—Observations on fifty cases of exophthalmic goiter followed for one year 1, first observations, 2, before operation, 3, after operation, 4, three months later, 5, six months later, 6, nine months later, and 7, twelve months later

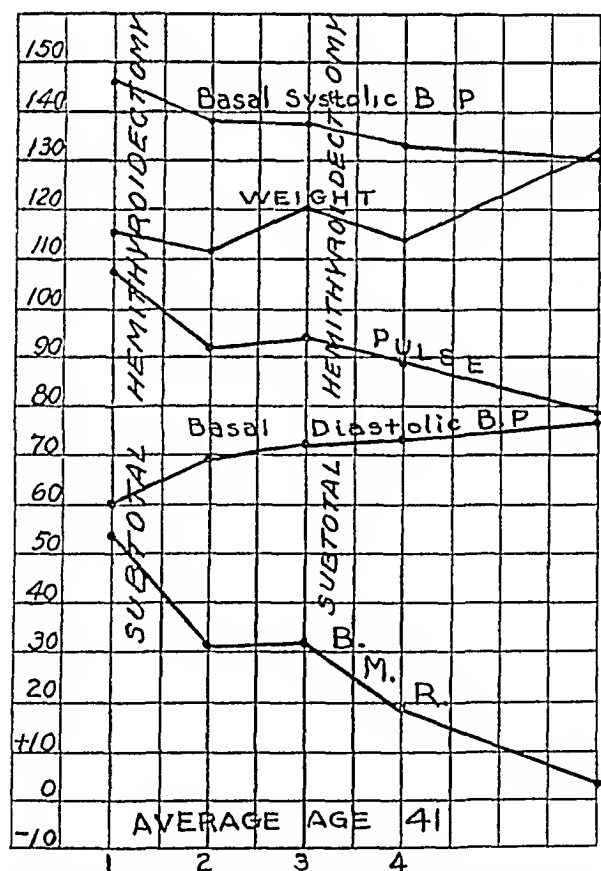


Chart 3—Observations on 100 cases of exophthalmic goiter requiring two stage operations 1, first observations, 2, after first operation, 3, before second operation (six weeks later), 4, after second operation, and 5, three months later

matous goiter with secondary hyperthyroidism. In these three groups there were no cases in which there was persistent or recurrent hyperthyroidism or postoperative myxedema. The average age of the patients requiring one-stage operations was 37.7 years, whereas the average age of patients requiring two-stage operations was 41.7 years. The average age of the adenomatous group was 51 years. While the pulse pressure and the rate of metabolism averaged higher in the patients who required two operations, this relationship did not hold true for the patients with

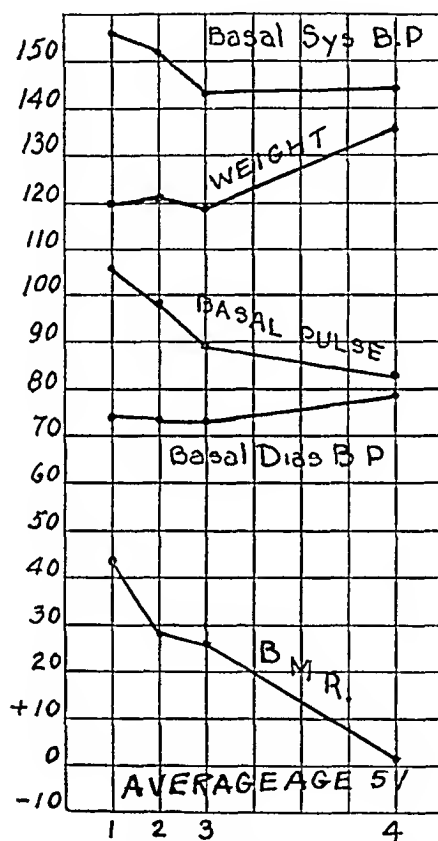


Chart 4—Observations on thirty-eight cases of toxic adenomatous goiter (average age, 51). 1, first observation before operation, 2, second observation before operation, 3, after operation, and 4, three months later.

adenomatous goiter. It was noted that the blood pressure in the adenomatous group was higher than that in the group with severe exophthalmos, yet the metabolic rate was lower. The difference in blood pressure in the three groups was probably due to the greater frequency of hypertension with advancing years.

In table 4 are shown the average blood pressure readings in 458 cases of toxic goiter in which a subtotal thyroidectomy was performed in one stage. This includes all cases in which there was persistent or recurrent hyperthyroidism or postoperative myxedema. They were

divided according to the length of time during which they had been observed

It may be noted from table 4, as well as from the preceding charts, that following operation there is a lower systolic pressure and a higher diastolic pressure. This also occurs before operation after a period of rest and the administration of compound solution of iodine. (All thyrotoxic patients in this study received compound solution of iodine, 10 minims [0.6 cc] three times a day irrespective of the type of goiter.) Of the cases requiring two operations, 46 per cent showed this change in blood pressure, i. e., a lower systolic pressure and higher diastolic pressure at the end of three months. However, 20 per cent showed an elevation of both the systolic and the diastolic basal blood pressures, while 14 per cent showed a reduction of both these blood pressures. The remainder had other minor variations. In the fifty cases of exophthalmic goiter

TABLE 4—*Basal Blood Pressure Observations on 458 Consecutive Cases of Toxic Goiter (All Types)*

Number of Cases	Average Basal Blood Pressure	Basal Blood Pressure				
	Before Operation	After Operation	In 3 Months	In 6 Months	In 9 Months	In 12 Months
46	132/69	131/74	129/76	123/77	124/76	122/76
53	137/72	130/73	131/78	129/77	126/76	
136	137/72	132/72	129/74	126/73		
193	138/69	131/71	129/81			
Total cases, 458						
Averages	137/70	131/70	129/77	126/77	125/76	122/76

which were followed with complete data for one year, 54 per cent showed a lower systolic and a higher diastolic pressure compared with that before operation, 26 per cent showed a lowering of both pressures, while 10 per cent showed an actual increase of both pressures. In thirty-eight cases of toxic adenomatous goiter, three months after operation, 40 per cent showed a lower systolic and a higher diastolic pressure, while 25 per cent showed both a lower systolic and a lower diastolic pressure, 21 per cent had a higher systolic and diastolic pressure after this interval.

In chart 5 is shown the effect of operation on the average basal blood pressures by decades in severe exophthalmic goiter (i. e., requiring two-stage operations), and in chart 6 is also shown the same effect in a group of 225 cases of all types of exophthalmic goiter selected to give reliable averages. The averages for the toxic adenomatous group before and after operation by decades are listed in tables 3 and 7.

One frequently sees patients with low or normal blood pressures who are toxic, emaciated, no longer markedly activated and even apathetic. These patients have a distinct rise in pressure when hyperthyroidism has been relieved. The explanation of this is difficult. The

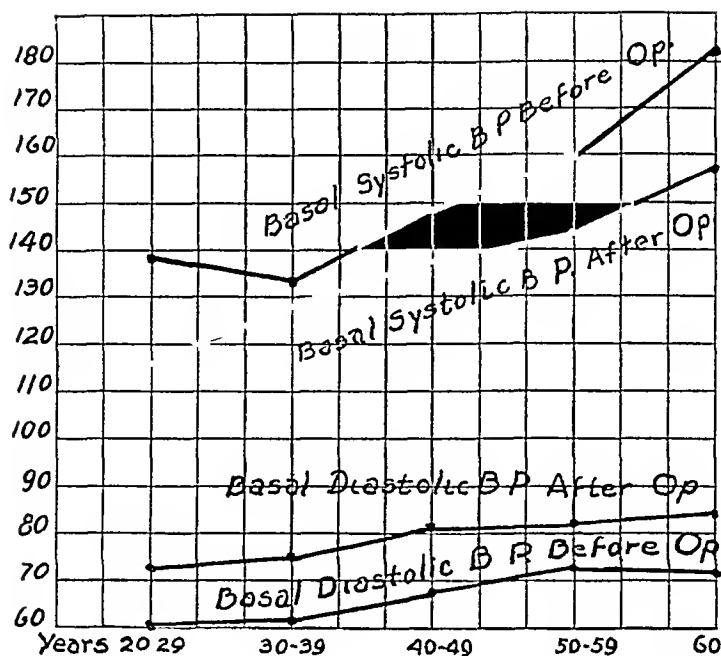


Chart 5—The average basal blood pressure before and after two-stage operation in different age groups in 100 cases of exophthalmic goiter

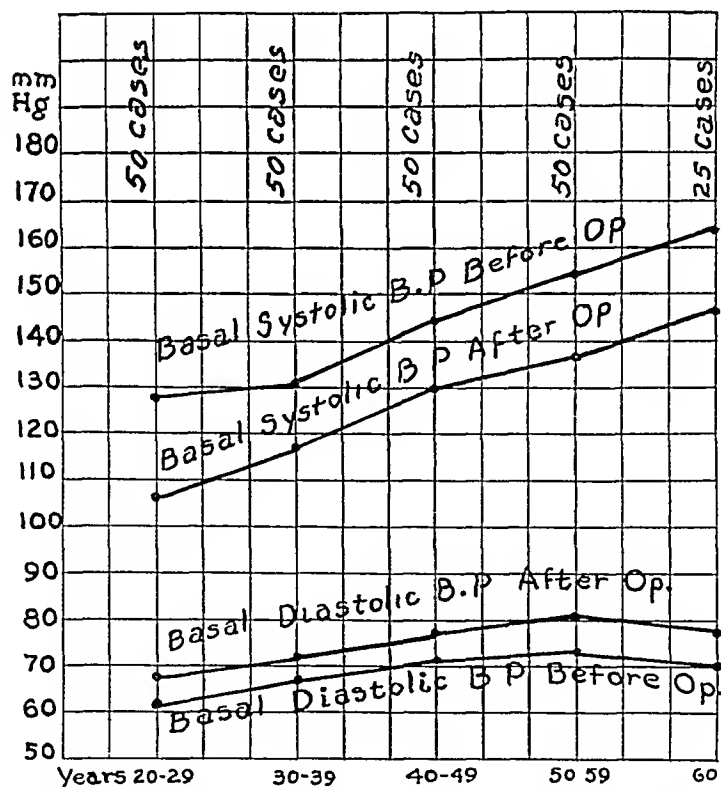


Chart 6—The basal blood pressure by decades of age in 225 cases of exophthalmic goiter, before operation and from six to twelve months after operation

observation that 20 per cent of the toxic patients had a rise in basal blood pressure following operation was surprising. Various factors may account for this. 1 A certain number had a prolonged rest in bed before coming to the hospital. 2 It is well known that a fall in blood pressure may take place when there is marked emaciation. 3 Some of these patients had an auricular fibrillation which returned to normal rhythm after the operation and permitted a more accurate determination of the blood pressure. I believe, however, that an auricular fibrillation may lower the blood pressure. Furthermore, the natural progression of an underlying hypertensive disease is a possibility.

The incidence of hypertension before and after operation in 458 cases of all kinds of toxic goiters is shown in table 5. An average basal blood pressure of 150 mm of mercury or more was present in 26 per

TABLE 5—*Analysis of Various Groups Before and After Operation in Relation to a Basal Systolic Blood Pressure of 150 Mm Hg*

Group	Per Cent Showing Systolic Blood Pressure of 150 Mm Hg or More Before Operation		Per Cent Showing Rise to 150 Mm Hg or Above After Operation	Average Age
	Before Operation	After Operation		
458 cases of all types average of blood pressure before operation	26.8	13.7 (3 mo. to 1 yr.)	4.8	37.1
100 cases of severe exophthalmic goiter initial blood pressure	42	23 (3 mo.)	11	41.2
50 cases of exophthalmic goiter initial blood pressure	26	6 (1 yr.)	0	37.8
54 cases of adenomatous goiter with hyperthyroidism initial blood pressure	62	44 (3 mo.)	7	51.2

cent of the cases before operation. From three months to a year following operation, 13.7 per cent still showed a basal pressure of 150 mm of mercury or more, 4.8 per cent in which the average blood pressure was under 150 mm of mercury before operation showed a final pressure higher than this figure. Thus, in this group of consecutive cases, approximately 18 per cent showed hypertension after operation. In the milder cases of exophthalmic goiter, 26 per cent showed an initial pressure of 150 mm of mercury or more on the first examination, whereas only 6 per cent showed a blood pressure of this degree at the end of a year. On the other hand, in the severe cases of exophthalmic goiter in which the basal metabolic rate was normal at the end of three months, 40 per cent showed an initial basal pressure of 150 mm of mercury or more before operation. At the end of three months, 23 per cent still had a basal systolic pressure of over 150 mm of mercury, while 11 per cent showed a rise from below this figure to above it. In the adenomatous group, 62 per cent showed an initial pressure of 150 mm of mercury

or more After three months, 44 per cent still showed this pressure and 7 per cent showed a rise to 150 mm of mercury or more These data are also recorded in table 5

The apparently higher percentage of hypertension in my cases of adenomatous goiter with hyperthyroidism may exist because of the greater age of the patients Approximately 20 per cent of the patients with exophthalmic goiter were over 50 years of age, whereas 50 per cent of the cases of adenomatous goiter occurred after 50 years of age

BLOOD PRESSURE AFTER OPERATION COMPARED WITH OTHER GROUPS

If one compares the average blood pressure readings of patients with toxic goiter after operation with those of other groups without goiter, the question of whether or not hyperthyroidism causes permanent vas-

TABLE 6—*Comparison of Average Clinical Blood Pressure by Decades*

Decade	Nongoitrous Patients		Nontoxic Goiter		1,000 Office Patients (Alvarez)		Diabetic Patients (Joslin)	
	No of Cases	Blood Pressure	No of Cases	Blood Pressure	Blood Cases	Blood Pressure	No of Cases	Blood Pressure
20 to 29	50	116/73	22	126/78	?	137*	50	111
30 to 39	50	120/77	61	133/84	?	130	50	124
40 to 49	50	137/81	52	150/90	Females	152	50	130
					Males	140		
50 to 59	50	143/82	54	154/90	Females	165	50	155
60 to 69	50	164/93	20	155/86	Males	153	50	154
					(Age group 50 to 74)			

* Systolic

cular hypertension should be at least partly answered Table 6 shows the average clinical blood pressures by decades of 250 nongoitrous persons seen in the clinic Tables given by Alvarez³ and Joslin⁴ are also shown Joslin's patients comprised both men and women Alvarez found that the blood pressure is approximately the same in men and women up to the age of 40, thereafter, a higher average was found for women In my group of nongoitrous persons, 82 per cent were women, an incidence approximately the same as in the goitrous persons In this table is also shown the average clinical blood pressures in goitrous patients who were considered nontoxic The average blood pressures are somewhat higher than in the nongoitrous persons in our clinic, but they parallel rather closely those in the women studied by Alvarez

3 Alvarez, W C, Wulzen, R, Taylor, F B, and Starkweather, E Blood Pressure in University Freshmen and Office Patients, Arch Int Med 26 381 (Oct) 1920

4 Joslin E C The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928, p 712

Table 7 shows the basal blood pressure in the same group of persons with nontoxic goiter as shown in table 2. Only with this group can comparisons be made with other groups, since the basal blood pressures are lower than those taken under the usual clinical conditions. In table 7 are placed for comparison the average basal blood pressures by decades in severe exophthalmic goiter, and in 225 cases of all grades of exophthalmic goiter, from 6 months to a year after operation (75 per cent were recorded at the end of a year). Thirty-eight cases of toxic adenomatous goiter before operation and at the end of three months are also included. It is to be noted (chart 7) that the averages of the 225 cases of exophthalmic goiter after operation parallel the averages of the cases of nontoxic goiter before operation. Thus, if the clinical blood pressures in the nontoxic cases parallel the clinical blood pressures of non-goitrous persons, there is no indication from this analysis that cure of

TABLE 7—*Comparison of Basal Blood Pressure in Cases of Nontoxic Goiter Before Operation and in Cases of Toxic Goiter After Operation (by Decades of Ages)*

Decade	Nontoxic Goiter Before Operation		Exophthalmic Goiter from 6 to 12 Mo After Operation		Exophthalmic Goiter 3 Mo After Operation (Severe)		Toxic Adenomatous Goiter 3 Mo After Operation	
	No of Cases	Blood Pressure	No of Cases	Blood Pressure	No of Cases	Blood Pressure	No of Cases	Blood Pressure
20 to 29	22	113/64	50	100/69	18	116/72		
30 to 39	61	117/40	50	118/72	23	128/75	8	124/69
40 to 49	52	131/77	50	130/77	26	137/81	11	129/76
50 to 59	54	144/82	50	137/81	27	143/82	19	153/83
60 to 69	20	141/80	25	147/77	4	158/83	9	156/88

exophthalmic goiter is followed by hypertension, at least not within from six months to a year later. The patients who required two operations show a higher residual average, but this is not a representative group. The presence of hypertension is often one of the reasons why an operation is done in two stages. The average basal postoperative blood pressures for the toxic adenomatous group are higher than those of the other groups in the fifth and sixth decades (chart 8). This is the only evidence pointing to the theory that hypertension may result from thyroid toxicity. It is doubtful if any conclusion can be based on 20 cases, and therefore this question is left open.

COURSE OF HYPERTENSION ASSOCIATED WITH HYPERTHYROIDISM

Chart 9 shows the course of fourteen patients with hypertension in whom basal and clinical blood pressure readings were obtained before operation and from six months to one year later. The patients were nontoxic clinically in spite of the fact that the average basal metabolic

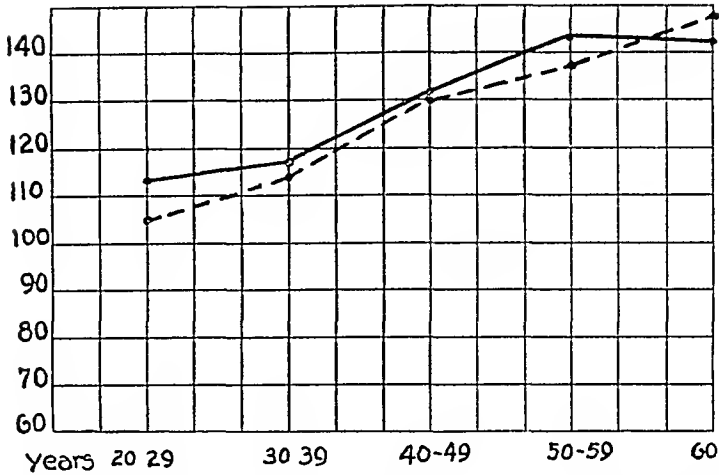


Chart 7—The average basal systolic blood pressure by decades of ages in cases of nontoxic goiter (solid line) before operation, and in cases of exophthalmic goiter (dash line) from six to twelve months after operation

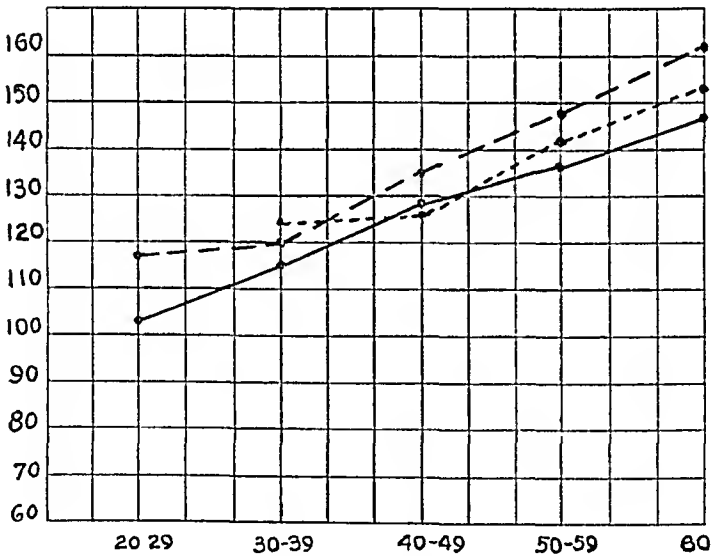


Chart 8—Comparison of readings of blood pressure by decades of ages in cases of goiter after operation and in nongoitrous persons The solid line indicates the exophthalmic group from six to twelve months after operation, the dash line office patients (nongoitrous) and the dotted line the toxic adenomatous group three months after operation

rate was slightly higher than in the other cured cases. Thirty-eight other cases of hypertension were selected in which the data for either basal or clinical blood pressure were complete, but not for both. The averages were essentially the same as those already given. Aside from the slight drop in the basal systolic blood pressure and a slight rise in the diastolic pressure, hypertension is unchanged by thyroidectomy if the increased pulse pressure produced by hyperthyroidism is eliminated. The average age of this group of patients was 52.

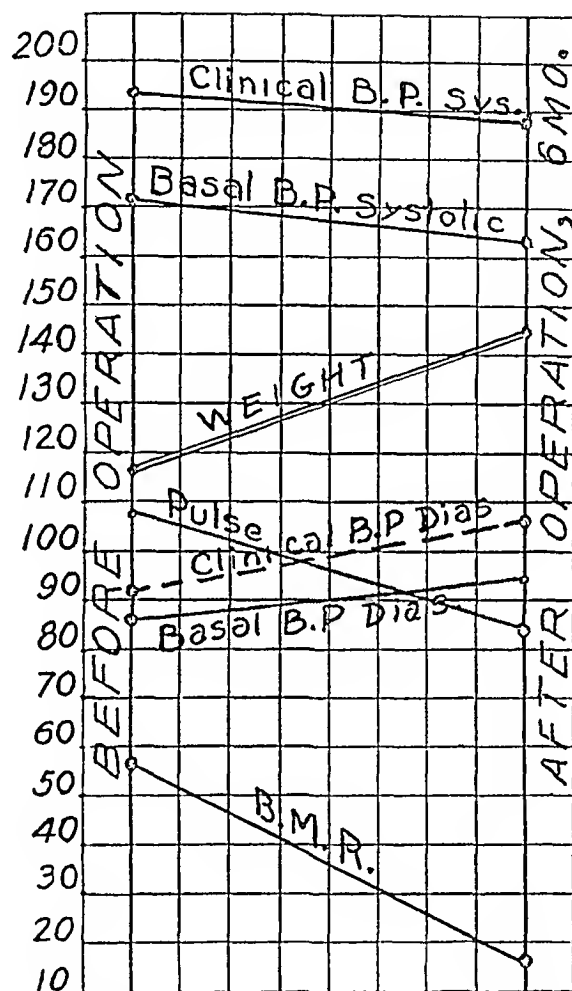


Chart 9—Average blood pressure in fourteen cases of hypertension and hyperthyroidism before, and six months or more after, operation

Another group of fourteen patients with toxic goiter who showed an auricular fibrillation before operation but a normal rhythm post-operatively and who were clinically free from thyrotoxic symptoms, was selected (chart 10). All these were considered hypertensive before operation. Only clinical blood pressures were recorded. The rise in both the systolic and the diastolic pressure was interesting and probably meant either that the blood pressure was lowered during the fibrillation of the auricles, or that the true pressure was not obtained. This may be

of some importance in individual cases, especially with congestive heart failure when associated with auricular fibrillation. An underlying hypertension may thus be overlooked.

OTHER OBSERVATIONS ON BLOOD PRESSURE

Mention should be made of the low or apparently absent diastolic pressure that is seen in extremely toxic cases. Pulsations may often be

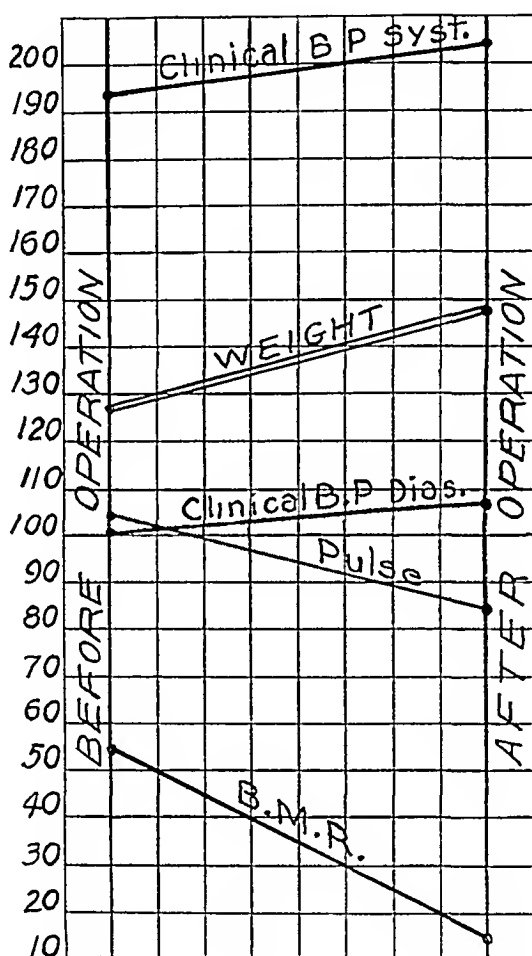


Chart 10—Average clinical blood pressure in fourteen cases of toxic goiter with auricular fibrillation and hypertension before operation, and six months or more after operation when normal rhythm was present

heard to the zero point. Whether or not this reading means an absent diastolic pressure is open to doubt. Occasionally, by simple adjustment of the stethoscope, a distinct change in sound may be heard in these cases between 30 and 60 mm on the scale.

The characteristic snapping sounds heard in hyperthyroidism when the blood pressure is taken are of great value in diagnosis. This is particularly true with borderline cases. This characteristic sound is

rarely found in hypertension alone or in other conditions in which an increased pulse rate is present. If a choice between blood pressure readings and the auscultatory sounds had to be made as an auxiliary aid to the diagnosis of hyperthyroidism, I feel that the latter would be of greater value.

CONCLUSIONS

1 The blood pressure readings taken under basal conditions are lower than those otherwise taken. The difference is most marked in patients with hyperthyroidism.

2 The pulse pressure is increased in hyperthyroidism and decreased in about 50 per cent of the patients following relief from thyroid toxicity.

3 On the basis of averages there is no constant relationship between the height of the systolic blood pressure and the basal metabolism rate.

4 The average height of the blood pressure increases with advancing age.

5 The average basal blood pressure readings in cases of toxic goiter after operation and in cases of nontoxic goiter before operation run parallel.

6 The average basal blood pressure reading following relief from hyperthyroidism in exophthalmic goiter and from toxic adenomatous goiter is approximately the same in each age group up to 50 years, but thereafter it is slightly higher in the toxic adenomatous group.

7 The blood pressure in hypertension complicated by hyperthyroidism undergoes, on an average, the same change that patients with hyperthyroidism without hypertension undergo following operation.

8 In hypertensive patients with auricular fibrillation and hyperthyroidism, the average blood pressure is higher after operation when thyroid toxicity has been relieved and the normal rhythm has been restored.

9 There is no evidence in this study from which it can be concluded that hyperthyroidism leads to permanent cardiovascular hypertensive disease.

FUNCTION OF THE LIVER IN DIABETES MELLITUS

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The intimate relationship of the liver to the pancreas, together with its association in carbohydrate metabolism, gives at least some justification for the assumption that hepatic dysfunction may be of frequent occurrence in diabetes mellitus. In an effort to corroborate or refute this supposition the function of the liver in 100 persons with diabetes has been studied.

A review of the literature shows that numerous articles have been written concerning hepatic function and tests for the estimation of it, but only a few investigators have reported determinations in diabetic patients. Joslin¹ stated

The liver is assuming more and more the prominent role which it played in diabetes in the time of Claude Bernard. Its influence for good or evil, perhaps measured by the amount of glycogen which it stores, is more and more acknowledged. Perhaps the great "factor of safety" which the liver possesses because of its size hides its importance in the etiology of diabetes.

The coexistence of cholecystitis and diabetes has been considered frequently. Opie² showed by animal experimentation and clinical observation that there is a definite relationship between cholelithiasis and diseases of the pancreas. Lichty and Woods³ endeavored to prove that cholecystitis was an etiologic factor in the production of diabetes. They reported 25 cases of diabetes and biliary tract disease in a series of 1,474 patients. Three of these apparently recovered from the diabetes after operations on the gallbladder. Adams⁴ reviewed 6,500 cases of gallbladder disease and 1,101 cases of diabetes. Both diseases were

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1 Joslin, E P. The Treatment of Diabetes Mellitus, ed 4, Philadelphia, Lea & Febiger, 1928, p 175.

2 Opie, E L. The Relationship of Cholelithiasis to Disease of the Pancreas and Fat Necrosis, Am J M Sc **121** 27, 1901.

3 Lichty, J A, and Woods, J O. The Significance of Glycosuria in Gall Bladder and Duct Disease, Am J M Sc **167** 1 (Jan) 1924.

4 Adams, S F. Is Disease of the Gall Bladder a Cause of Diabetes Mellitus? Surg Gynec Obst **41** 75 (July) 1925.

present in 131 patients, all of whom were over 40 years of age Wilder ⁵ reported 20 cases of biliary tract disease in 58 diabetic patients examined post mortem Sixteen of these had calculi

Joslin ¹ remarked

Gallstones are about 50 per cent more common among diabetics over 25 years of age than among a similar group in the community at large Gallstones often precede diabetes and may precipitate it by direct extension of infection to the head of the pancreas Diabetes is not only due to a disturbance of carbohydrate metabolism, but, as shown by Pfluger, Geelmuyden and Allen, an associated protein and fat disturbance

In four Boston hospitals 211 necropsies were performed on diabetic patients over 25 years of age Fifty of these, or 23.7 per cent, had gallstones Bowen, Vaughan and Koenig ⁶ reported that from 1923 to 1928 at the Buffalo General Hospital 16 autopsies were performed on adult diabetic patients, and that of these 1 showed calculi and 3 cholecystitis Surgeons are constantly observing at operation that all cases of chronic cholecystitis are associated with varying degrees of hepatitis and not infrequently with pancreatitis Rabinowitch ⁷ said

There is much clinical and statistical evidence to prove that the association of diabetes and gallbladder disease is more than accidental, and that pancreatitis is generally recognized as a sequela of cholelithiasis and cholecystitis

Jones, Castle, Mulholland and Bailey ⁸ investigated pancreatic and hepatic activity in sixty-eight cases of diabetes mellitus They discovered diminished pancreatic activity in one half of the cases and abnormally high elimination of bile pigment in the duodenal contents in three fourths of the cases They decided that undernutrition had an undesirable effect on both liver and pancreas, but that when this was controlled by efficient insulin therapy and diet there was a marked reduction in the pancreatic and hepatic abnormalities Cholelithiasis occurred in 19 per cent of the cases The average age of the patients was 51

Rabinowitch ⁷ studied hepatic function in 130 cases of diabetes mellitus He considered the phenoltetrachlorophthalein test insufficiently sensitive for the detection of early impairment of liver efficiency In only 3 of 50 cases was the Wallace and Diamond method for estimations

5. Wilder, R. M. Necropsy Findings in Diabetes, *South M. J.* **19** 241 1926

6. Bowen, B. D., Vaughan, S. L., and Koenig, E. C. The Relation of Liver and Gall Bladder Disease to Diabetes, etc., *Bull. Buffalo Gen. Hosp.* **6** 41 (Dec.) 1928

7. Rabinowitch, J. M. The van den Bergh Reaction in Diabetes *Brit. J. Exper. Path.* **7** 155, 1926

8. Jones, C. M., Castle, W. B., Mulholland, H. B., and Bailey, Francis. Pancreatic and Hepatic Activity in Diabetes Mellitus. The Alterations with Some Observations on the Etiology of the Disease, *Arch. Int. Med.* **35** 315 (March) 1925,

of urobilinogen in the urine found to give positive results. The indirect van den Bergh test was employed in all the cases. The results were not expressed in milligrams or units, but were referred to as positive when the colors were of greater intensity than normal. Thirty-four, or 26.1 per cent, had a positive van den Bergh reading, and the percentage of positive reactions was twice as great in the overweight subjects.

Diamond⁹ performed the van den Bergh test in a large series of cases. In seventeen of these diabetes mellitus was present. Fourteen gave normal results. Three of the more severe cases in which no treatment had been given gave high readings for bilirubin: 1.1 units, 1.2 units and 1.4 units, or, expressed in milligrams per hundred cubic centimeters, 0.55, 0.6 and 0.7. He also found a high excretion of urobilinogen during acidosis and a return to normal with the administration of insulin. He concluded that despite the diversity of the functions of the liver a high value for blood bilirubin indicates a disturbance of the liver, unless due to hemolytic disease.

Bowen, Vaughan and Koenig⁶ estimated hepatic function in twenty-three cases of diabetes mellitus. In none of these cases did the urobilinogen in the urine exceed 1:20, and only seven gave this reading. They evidently considered the finding of urobilinogen in this dilution indicative of hepatic dysfunction. The result of the quantitative van den Bergh test exceeded 0.6 units (0.3 mg) in twelve cases, and 1 unit (0.5 mg) in eight cases. Bromsulphalein retention was present in five patients, but the test was performed in only fourteen cases of diabetes. The lowest reading for blood sugar was 115 mg, the highest 548 mg and the average 221 mg. They concluded that tests for hepatic dysfunction more regularly give positive results in cases of diabetes than in the group of alimentary glycosuria.

METHODS

The 100 diabetic persons were studied in the metabolic wards of the Philadelphia General Hospital. They were first examined and treated by the chief of the metabolic department and his associates. A history was taken of each patient, and a complete physical examination conducted, with all the usual or specially indicated laboratory tests. Later, studies of hepatic function were instituted. The urobilinogen, bromsulphalein retention, icterus index and direct and indirect van den Bergh tests were selected as the most satisfactory in the study of diabetic persons, and were used to obtain data concerning every member. All tests were conducted and blood specimens obtained early in the morning before the patients received breakfast. Studies of cholesterol were also done in the hope that some additional information would be obtained concerning cholesterol metabolism and its value in the prognosis of diabetes, as indicated by the 2,000 estimations reported by Rabinowitch.¹⁰

9 Diamond, J. S. The Value of Routine Estimations of Blood Bilirubin, *Am J M Sc* **176** 321, 1928.

10 Rabinowitch, J. M. Cholesterol Content of Blood Plasma in Diabetes Mellitus, *Arch Int Med* **43** 372 (March) 1929.

The Wallace and Diamond¹¹ technic was used for estimations of urobilinogen. A series of accurate dilutions of urine was made, and only those readings were recorded that showed a definite pink color. Warm water was used in diluting the urine, and the final reading was made five minutes after adding the Ehrlich reagent. The specimens examined were usually portions of the preceding twenty-four hours' output. The urine was placed in covered mason jars containing toluol. They were kept in electrically operated refrigerators at 42 F. It was found that when urine is exposed to heat and light the value of the test decreases proportionately with the time elapsing after voiding. Samples examined soon after urination, or at different periods of the day, rarely furnished information greater than that obtained from properly cared for twenty-four hour specimens. A positive reaction in urine diluted more than twenty times was considered abnormal.

The bromsulphalein test as reported by Rosenthal and White¹² was found to be extremely satisfactory and without hazard of venous thrombosis or prolonged discomfort to the patient. A 5 per cent solution of 2 mg of the dye per kilogram of body weight was slowly injected. A 5 cc syringe was used and a twenty-four gage hypodermic needle, and when the injection was completed, about 5 cc of blood was drawn into the syringe and re-injected, all of the dye being thus obtained and also the deposit of bromsulphalein about the wall of the vessel or adjacent tissues on withdrawal of the needle being prevented. A specimen was obtained exactly thirty minutes later, and any retention was considered indicative of hepatic dysfunction.

The icterus index was computed according to the Beinheim method,¹³ modified by Murphy¹⁴. The test is easily performed, but unless extreme care is observed in collecting blood specimens and obtaining the serum subsequently, it is impossible to make accurate estimations. As a result of the large pigment content in the diabetic diet and the frequency of lipemia during the course of the disease, an accurate interpretation of the icterus index is often impossible. It was found more satisfactory to dilute the serum before reading with a phosphate buffer (p_H 7.4) than with physiologic solution of sodium chloride. In my opinion, the icterus index is a less reliable test in diabetic patients than the quantitative van den Bergh test.

The qualitative van den Bergh test was read at the time of adding the diazo reagent to the serum, as directed in the quantitative method of Thannhauser and Anderson¹⁵. The last procedure of their technic was modified by using cobalt standards in small test tubes and after centrifugation withdrawing the supernatant

11 Wallace, G. B., and Diamond, J. S. The Significance of Urobilinogen in the Urine as a Test for Liver Function, with a Description of a Simple Quantitative Method for Its Estimation, *Arch. Int. Med.* **35**: 698 (June) 1925.

12 Rosenthal, S. M., and White, E. C. Clinical Application of the Bromsulphalein Test for Hepatic Function, *J. A. M. A.* **84**: 1112 (April 11) 1925.

13 Bernheim, A. The Icterus Index (A Quantitative Estimation of Bilirubinemia), Aid in Diagnosis and Prognosis, *J. A. M. A.* **82**: 291 (Jan. 26) 1924.

14 Murphy, W. P. An Easy Method of Estimating the Amount of Jaundice by Means of the Blood Serum, *Boston M. & S. J.* **194**: 297, 1926.

15 Thannhauser, J. R., and Anderson, E. Methodik der quantitativen Bilirubin Bestimmung in menschlichen Serum, *Deutsches Arch. f. klin. Med.* **137**: 179, 1921.

fluid into similar test tubes and then reading rather than attempting a comparison in the centrifuge tubes

Wallace and Diamond,¹¹ Eusterman,¹⁶ Hall,¹⁷ Piersol and Rothman,¹⁸ Graham, Cole and Copher¹⁹ and Foley²⁰ offer abundant data to indicate the value of these tests for the estimation of hepatic function and to aid in the interpretation of the results

The normal results in the selected tests have been satisfactorily determined. All investigators agree that the retention of any bromsulphalein after thirty minutes should be considered abnormal and indicative of hepatic disease. Foley²⁰ examined 100 persons from the outpatient department of the Research and Educational Hospital. They were apparently free from gross pathologic changes of the liver. He stated, "Particular attention was taken to exclude cases in which a history of alcoholism or syphilis was obtained." Not one of these had any bromsulphalein retention after thirty minutes.

An icterus index reading of from 3 to 6 is accepted as the usual normal, and 99 per cent of Foley's²⁰ cases had 6 or less.

A positive reaction for urobilinogen in urine diluted twenty times is taken as the high normal. Piersol and Rothman¹⁸ considered this the most delicate test for hepatic function and any elevation greater than 1/20 indicative either of hepatic injury or of excessive production of bilirubin.

The quantitative van den Bergh reaction is subject to greater variations in interpretation as to normal values. The average range is usually given as from 0.1 to 0.25 mg or 0.3 mg per hundred cubic centimeters. Van den Bergh,²¹ McNee,²² Hall,²³ Ravdin,²⁴ Roberts,²⁵

16 Eusterman, G. B. Functional Tests of the Liver, a Clinical Review, *Ann Int Med* **1** 53 (Aug) 1927.

17 Hall, W. W. The van den Bergh Reaction for Serum Bilirubin, with Notes on Interpretation and Technique, *J Lab & Clin Med* **12** 529, 1927.

18 Piersol, G. M., and Rothman, M. M. The Practical Value of Liver Function Tests, *J A M A* **91** 1768 (Dec 8) 1928.

19 Graham, E. A., Cole, W. H., Copher, G. H., and Moore, S. Diseases of the Gall Bladder and Bile Ducts, Philadelphia, Lea & Febiger, 1928, pp 337-398.

20 Foley, E. F. Liver Function Tests, *Arch Int Med* **45** 302 (Feb) 1930.

21 van den Bergh, A. A. H. Jaundice, *Brit M J* **2** 498 (Sept) 1924.

22 McNee, J. W. Jaundice, Review of Recent Work, *Quart J Med* **16** 390, 1923.

23 Hall, W. W. Useful Hepatic Function Tests, *U. S. Nav. M. Bull* **24** 843, 1926.

24 Ravdin, E. G. Clinical Value of the van den Bergh Test, *Am J M Sc* **169** 850, 1925.

25 Roberts, W. M. Observations on the Nature of the van den Bergh Reaction, *Brit J Exper Path* **9** 107, 1928.

Andrews,²⁶ Anderson,²⁷ Rhamy²⁸ and Graham, Cole and Copher¹⁹ agreed with these figures. Perkin,²⁹ after examining 50 presumably healthy persons, decided that from 0.05 to 0.35 mg would include all normal cases. Diamond⁹ gives from 0.2 to 0.4 mg. Schiff,³⁰ after examining 202 persons, concluded that a reading over 0.6 mg is abnormal and said, "When higher values are quoted it is to care for cases of familial cholemia." Rowntree³¹ and Greene, Snell and Walters³² gave from 0.2 to 1 mg and from 0.5 to 2 mg, respectively as the normal range. In Foley's 100 clinical cases, 71 per cent showed less than 0.3 mg and 95 per cent less than 0.5 mg.

Apparently there are sufficient data to conclude that from 0.25 to 0.3 mg may be safely taken as the usual high normal.

EXPERIMENTAL DATA

After completing the investigations on the 100 diabetic patients three main groups, A, B and C, were formed for study and comparison.

Group A—The forty-eight members of group A afforded neither physical observations nor laboratory evidence indicative of dysfunction of the liver.

Group B—The thirteen patients of group B could have been included in group A if nine (subgroup B-1) had not shown a very slight retention of bromsulphalein. This amount did not definitely measure 3 per cent and was recorded as from 0 to 3 per cent, thus indicating that the amount was too small to be estimated accurately and possibly would be ignored by some investigators or classified as a trace. The remaining four (subgroup B-2) showed only an elevated van den Bergh value. Two had 0.4 mg and the others 0.5 mg. As this was the only indication of hepatic dysfunction, it is probable that the readings should not be considered abnormal in these cases.

26 Andrews, C. H. A Clinical Study of the van den Bergh Test in Jaundice, *Quart. J. Med.* **18** 19, 1924.

27 Anderson, J. H. Examination of the Blood for Bile Pigment, *Lancet* **2** 346, 1929.

28 Rhamy, B. W. Estimation of Bilirubin in the Blood as an Index of Liver Function, *J. Indiana M. A.* **20** 212, 1927.

29 Perkin, F. S. Blood Bilirubin, Estimation and Clinical Significance, *Arch. Int. Med.* **40** 195 (Aug.) 1927.

30 Schiff, Leon. Serum Bilirubin in Health and in Disease, *Arch. Int. Med.* **40** 800 (Dec.) 1927.

31 Rowntree, L. G. Our Present Knowledge of Test of Liver Function, *Proc. Inter-State Post-Grad. M. Assemb., North America*, 1927, **3** 475, 1928.

32 Greene, C. H., Snell, A. M., and Walters, Waltman. Diseases of the Liver. I. A Survey of Tests for Hepatic Function, *Arch. Int. Med.* **36** 248 (Aug.) 1925.

Group C—From the thirty-nine patients in group C it was possible to obtain evidence indicative of hepatic dysfunction. At least one test in each case gave a positive result.

The special table with the individual laboratory data for group A is omitted, as the results of all the tests employed in the estimation of the hepatic function were interpreted as normal. With foci of infection in teeth, tonsils and sinuses excluded, all persons in group A were considered as having uncomplicated diabetes mellitus, except as follows. Patients 26 and 62 both had had cholecystectomies performed five years

TABLE 1—Data on Patients in Group B

Pa- tient	Sex	Age	Weight		Duration of Diabetes, Yr	Units of Insulin Daily	Blood Dextrose, Mg	Cholesterol, Mg	Urobilinogen (Urine Dilution)	Icterus Index	Result, Qualita- tive van den Bergh Test	Mg Bilirubin, Quantitative van den Bergh Test	Bromsulphalein Retention, %
			Lb	Kg									
Subgroup B 1													
17	F	45	309	140.1	2	140	145	170	None	4	Negative	0.2	0-3
31	M	71	192	87.1	0.5	13	155	140	1 20	6	Faint delay	0.3	0-3
36	M	50	132	59.9	1	25	120	220	1 10	4	Faint delay	0.3	0-3
37	M	51	155	70.3	12	20	97	250	1 20	6	Faint delay	0.3	0-3
40	F	55	137	62.1	1	54	102	135	1 1	6	Negative	0.3	0-3
80	M	57	113	51.3	5	5	97	240	1 20	6	Negative	0.3	0-3
81	F	68	152	68.9	6	9	93	235	1 20	4	Negative	0.2	0-3
45	F	42	123	55.8	1	69	130	175	1 1	4	Negative	0.1	0-3
86	M	31	99	44.9	0.5	0	96	180	1 1	2	Negative	0.0	0-3
Average		52	156.8	71.2	3.1	37.2	115	193.8	1 10	4.6	6 negative 3 faint delay	0.22	0-3
Subgroup B 2													
3	M	18	140	63.5	4	133	260	140	1 20	4	Negative	0.4	0
19	M	70	146	66.2	6.5	27	137	140	1 10	6	Faint delay	0.4	0
66	M	39	160	72.6	5	35	251	160	1 10	8	Faint delay	0.3	0
87	F	55	131	59.4	1	48	234	200	1 10	8	Faint delay	0.5	0
Average		45.5	144	65.3	4	60.7	220	166	1 12	6.5	1 negative 3 faint delay	0.45	0

Additional average results for subgroup B 1 were urea nitrogen, 14.4 mg, carbon dioxide, 52.4, hemoglobin, 13.2 Gm. Wassermann reactions, negative.

Additional average results for subgroup B 2 were urea nitrogen, 14.7 mg, carbon dioxide, 49.5, hemoglobin, 15.1 Gm, Wassermann reactions, negative.

prior to these tests. Multiple calculi were present in each case. Patient 26 was a woman, 43 years of age, in whom diabetes had been diagnosed three years after operation. At the time of examination she was apparently well and required ten units of insulin and a prescription diet. Patient 62 was a woman, 58 years of age in whom diabetes was diagnosed at the time of operation. This patient had used extremely large doses of insulin for a year previous to the tests. It was necessary to have her under constant observation to prevent acidosis which was present five times prior to continuous hospitalization. Patient 88 was a woman, aged 65, who entered the hospital with gangrene of the foot and it was necessary to amputate the thigh. The tests were performed just prior to her departure from the hospital. Patient 92 was a man,

20 years of age, who had advanced pulmonary tuberculosis with cavity formation in both upper lobes. While in the hospital, he gained weight and improved markedly. Patient 97 was a man, aged 41, who had had progressive muscular distrophy for two years and apparently during the past six months had shown some general improvement. Patient 99 was a woman, aged 47, who had used alcohol excessively for several years. She had been treated in the women's psychopathic department for three months prior to her transference to the metabolic wards for study.

The individual data in group B are given in table 1. Patient 17 of this group was an extremely obese woman weighing 309 pounds (140.1 Kg). In addition to 140 units of insulin, she was taking 2 grains of thyroideum siccum daily. Patient 45 was a woman, aged 42, who

TABLE 2—Data on Patients in Group C—Subgroup 1

Patient	Sex	Age	Weight		Duration of Diabetes, Yr	Units of Insulin Daily	Blood Dextrose, Mg	Cholesterol, Mg	Urobilinogen (Urine Dilution)	Icterus Index	Result, Qualitative van den Bergh Test	Mg Bilirubin, Quantitative van den Bergh Test	Bromsulphalein Retention, %
			Lb	Kg									
5	F	33	106	48.1	1	5	104	190	1:300	100	Immediate	8.0	100
35	M	37	137	62.1	0.25	15	100	195	None	160	Biphasic	20.0	58
36	M	68	130	59	3	15	140	160	1:200	60	Immediate	11.0	70
61	M	49	120	54.5	2	15	129	157	1:100	6	Biphasic	0.2	40
39	M	43	105	47.8	0.5	42	118	125	1:50	6	Negative	0.3	5
69	F	48	150	68	0.5	38	139	120	1:50	5	Negative	0.3	10
98	F	60	137	62.1	2	55	125	160	1:200	6	Negative	0.3	10
50	M	67	129	58.5	2	65	157	150	1:50	6	Negative	0.3	0
12	F	75	138	62.6	1	8	166	135	1:50	2	Negative	0.0	25
13	F	36	134	60.8	1	40	113	160	1:10	4	Negative	0.0	15
90	F	39	133	60.3	1	5	71	170	1:50	4	Negative	0.1	0
Average			52.2	135.1	61.25	1.3	25.7	124.1	157				

Additional average results were: urea nitrogen, 27 mg (high from three cases of nephritis), carbon dioxide, 49.7, hemoglobin, 12.6 Gm., albumin present in all specimens of urine, Wassermann reaction, negative in all cases except no. 50.

had an infected finger that was later amputated. She had a leukocyte count of over 10,000 and required 69 units of insulin daily. Patient 86 was a man, aged 31, who had a severe form of xanthoma associated with profound secondary anemia. The hemoglobin was 10.1 Gm and the erythrocytes 2,300,000. Patient 3 had been in coma five times. He was uncooperative and frequently failed to observe his diet.

The thirty-nine members of group C were placed in two groups. C-1 was composed of eleven patients, seven of whom showed clinical manifestations of hepatic dysfunction, one syphilis and three nephritis. Data on these are given in table 2. C-2 included the remaining twenty-eight patients. Not one of these afforded clinical evidence (except laboratory) of hepatic injury. It was impossible to demonstrate any complicating factor that could influence the tests for hepatic function. For data concerning these patients, see table 3.

In group C-1, the case of patient 5 was diagnosed as catarrhal jaundice. This condition appeared four months after the removal of infected teeth and tonsils, which was done with the hope of improving the diabetic condition. The selected tests were done frequently, and there was gradual improvement. She was discharged four weeks after hospitalization and six weeks after the onset of jaundice. At this time urobilinogen was present in a dilution of 1:50, there was bromsulpha-

TABLE 3—Data on Group C—Subgroup 2

Pa- tient	Sex	Age	Weight		Duration of Diabetes, Yr	Units of Insulin Daily	Blood Dextrose, Mg	Cholesterol, Mg	Urobilinogen (Urine Dilution)	Icterus Index	Result, Qualita- tive van den Bergh Test	Mg. Bilirubin, Quantitative van den Bergh Test	Bromsulphalein Retention, %
			Lb	Kg									
4	M	61	158	71.7	5	0	93	180	1:20	6	Negative	0.3	5
22	M	52	165	74.8	15	30	96	180	1:20	4	Negative	0.2	5
42	F	55	135	61.2	3	45	158	160	1:10	6	Faint delay	0.3	8
44	F	46	131	59.4	1	69	185	155	1:20	4	Negative	0.1	3
51	F	60	135	61.2	?	37	141	200	1:10	4	Negative	0.1	3
52	F	53	88	39.4	3	57	109	242	1:20	5	Negative	0.2	8
72	M	37	138	62.6	1	54	178	160	1:10	4	Faint delay	0.2	10
73	M	74	130	59	0.5	30	169	200	1:10	4	Faint delay	0.2	8
75	F	73	134	60.8	16	8	140	150	1:1	4	Faint delay	0.2	3
76	F	70	134	60.8	25	120	237	210	1:10	6	Negative	0.3	3
77	M	68	144	65.3	5	5	105	185	1:10	4	Negative	0.1	3
83	F	64	115	52.1	1	60	237	180	1:10	4	Negative	0.1	3
84	M	61	98	44.5	1	40	144	165	1:20	5	Faint delay	0.5	5
85	F	52	145	65.8	1	40	132	190	1:20	4	Negative	0.2	8
91	F	61	140	63.5	1	76	183	150	1:20	6	Negative	0.3	3
94	M	65	118	53.5	1	8	97	160	1:10	4	Negative	0.0	13
41	M	54	165	74.8	7	10	122	155	1:10	8	Negative	0.4	5
54	M	55	179	81.2	1	15	118	180	1:20	6	Negative	0.5	5
18	M	49	148	67.1	3	15	183	165	1:50	12	Faint delay	0.7	25
34	M	62	136	61.7	1	3	104	165	1:50	8	Faint delay	0.5	10
82	M	67	134	60.8	7	20	138	175	1:50	10	Faint delay	0.6	3
10	M	54	198	89.8	2	40	143	135	1:50	5	Faint delay	0.5	0-3
24	M	28	110	54	1	25	118	150	1:50	8	Faint delay	0.5	0-3
70	M	70	105	46.7	2	3	142	140	1:50	10	Faint delay	0.5	0-3
7	M	52	126	57.2	7	39	183	240	1:50	12	Faint delay	0.5	0
11	M	43	129	58.5	?	35	278	160	1:100	4	Faint delay	0.3	0
30	M	40	126	57.2	2	20	260	170	1:50	8	Negative	0.3	0
67	M	42	115	52.1	10	27	152	165	1:50	6	Negative	0.2	0
Average			52.2	133	60.3	3.3	159.7	173.3	1:28	6	15 negative 13 faint delay	0.3	5.5

Additional average results were: urea nitrogen, 112 mg; carbon dioxide, 51.8; hemoglobin, 13.3 Gm; Wassermann reactions, all negative.

lecin retention, 20 per cent, the icterus index was 60, the van den Bergh reaction was biphasic and showed 3 mg of bilirubin, there was 190 mg of cholesterol.

Patient 35 was a man who had been in good health and apparently free from diabetes. He gave a history of symptomless jaundice which had been gradually increasing for three months. At this period, he entered the hospital, and it was found that 15 units of insulin were necessary to control the hyperglycemia. The various tests were performed frequently. There was a total absence of urobilinogen, both in urine and in duodenal contents, at all times. The last bromsulphalein test showed 65 per cent retention, the icterus index was 100, the van den

Bergh reaction was biphasic, and showed 10 mg of bilirubin. An exploratory operation showed an extensive carcinoma of the pancreas, causing complete occlusion of the biliary passages. The autopsy four weeks later corroborated the operative diagnosis.

Patient 56 was a man who had had diabetes for over three years. He entered the hospital on account of a severe nasal hemorrhage. He then also afforded clinical evidence of portal cirrhosis. It was necessary to perform paracentesis abdominalis three times. He gradually improved, and when discharged showed urobilinogen, 1/20, bromsulphalein retention, 35 per cent, icterus index, 25, and van den Bergh reaction, biphasic, and showed 1.5 mg of bilirubin.

Patient 61 was unusually interesting. Eleven years before these studies, he entered the Philadelphia General Hospital with anasarca and a diagnosis of alcoholic cirrhosis was made. He improved. Three years before these tests diabetes developed. In January, 1929, he had an amputation of the thigh for gangrene of the foot and leg. He improved and was discharged to the metabolic clinic. Jaundice first appeared on July 1, 1929. At this time, there was no urobilinogen in the urine, and the van den Bergh reaction was an immediate direct reaction, with 21 mg of bilirubin. Daily examinations showed little change until the sixth day, at which urobilinogen could be detected in undiluted urine. The van den Bergh test showed 15 mg of bilirubin. On the twelfth day, urobilinogen was present in a dilution of 1/20. The van den Bergh reaction was biphasic, with 15 mg of bilirubin. On Aug. 2, 1929, Talma's operation was performed and a section of the liver removed for study. The pathologic report was adenoma of the parenchyma of the liver. On October 22, urobilinogen was present 1/100, there was 40 per cent retention of bromsulphalein, the icterus index was 6, the van den Bergh reaction, direct, was negative, indirect, 0.2 mg. On Jan. 7, 1930, the urobilinogen was present in a dilution of 1/10, there was 20 per cent retention of bromsulphalein, the icterus index was 8, the van den Bergh reaction was very faintly biphasic with 0.3 mg of bilirubin. At this time, the patient was clinically improved.

Patient 59 was a man who had been using alcohol to excess for at least two years prior to entering the hospital. The liver was palpable and definitely enlarged. He also had oral sepsis and peripheral neuritis of the right foot and leg. Treatment directed toward his diabetic condition caused a gradual improvement. At the end of ten weeks, he was apparently normal, except for diabetes mellitus.

Patient 69 was a woman who entered the hospital for gallbladder disease associated with jaundice. The diabetic condition was discovered prior to operation, at which carcinoma of the liver and biliary tract was

diagnosed Drainage was instituted, but the patient gradually succumbed Death was undoubtedly hastened by multiple abscesses of the back

Patient 98 was a woman who seven years previously had an amputation of the breast because of carcinoma Four years later, diabetes developed, which required 55 units of insulin daily She returned to the hospital in December, 1929, on account of marked dyspnea Physical signs suggested carcinoma of the lungs This diagnosis was supported by roentgenograms, and also by the removal of a sanguineous pleural effusion She felt improved and insisted on leaving the hospital Death occurred shortly thereafter, but it was impossible to obtain permission for an autopsy Probably the liver also contained metastatic carcinoma

Patient 50 had a severe grade of diabetes A year previously gangrene of the foot and leg necessitated amputation of the thigh The patient had a tour plus Wassermann reaction and furnished evidence permitting the diagnosis of *tabes dorsalis*

Patient 12 had a severe nephritis in addition to diabetes The bromsulphalein and urobilinogen tests both yielded positive results The erythrocytes were 2,500,000, the leukocytes, 12,500 The hemoglobin content was 7.8 Gm Death occurred forty-eight hours after admission to the hospital

Patients 13 and 90 also were nephritic Studies of the liver were conducted at least two months after hospitalization At this time, the condition of the kidneys had markedly improved, and the diabetes was well controlled Patient 13 had the severe type of diabetes, and patient 90 showed greater renal dysfunction The hemoglobin readings were 11.5 and 11.8, respectively It is interesting to note in this connection that the van den Bergh readings were lower than normal in all of these nephritic persons with secondary anemia

The members of subgroup C-2 require only brief comment They were all well standardized and apparently free from complications at the time of examination Seven patients, nos 18, 51, 70, 75, 77, 84 and 94, entered the hospital with gangrenous feet and legs, and it was necessary to perform unilateral amputations of the thigh These patients all improved rapidly, but none of them was studied until recovery was practically complete

Patient 11 was jaundiced for seven months about four years before these studies He was finally referred to the metabolic department with the diagnosis of diabetes mellitus and carcinoma of the liver Under a strict diabetic regimen, he apparently returned to normal (except for diabetes) and has been able to work continuously as a hospital orderly for over three years It seems justifiable to assume that the diagnosis of carcinoma was an erroneous one

COMMENT

The forty-eight members of group A offered neither clinical manifestations nor laboratory evidence of hepatic dysfunction. It was expected that the studies of hepatic function in three of the cases (that of the alcoholic person and the two of patients who had cholecystectomies) would give positive observations, but these remained within a normal range. Undoubtedly, the great size of the liver at all ages amply provides for the numerous hepatic functions, and also affords a "factor of safety" sufficient to care for a considerable degree of injury, thus making the estimation of minimal hepatic dysfunction an unusually difficult problem. It seems reasonable to assume that any evidence of damage to the liver when obtained by approved tests, carefully performed, should be considered of diagnostic import. In addition, these studies were all conducted on patients using accurately weighed prescription diets. All were fairly well standardized, and in group A all but one required insulin. Jones, Castle, Mulholland and Bailey⁸ concluded that the better the diabetes is controlled the less apparent hepatic dysfunction becomes. This coincides with the impression gained in this series. Undoubtedly, the rigidly enforced regimen (embracing as it does a well balanced, nutritious diet, rich in vitamins, minerals and base-producing foods, insulin as required, proper rest and exercise, and general prophylactic and hygienic measures) contributes in a great measure toward hepatic regeneration and the restoration of normal function.

In group B, the retentions of bromsulphalein, even though extremely slight, might be considered sufficient data to classify these patients as having hepatic dysfunction. As the amount of dye retained could not be accurately measured, these patients, as well as those with only the slightly elevated van den Bergh readings, will not be considered as showing definite hepatic dysfunction, but are presented merely for consideration.

The thirty-nine patients in group C all furnished laboratory data interpretable as evidence of hepatic dysfunction. As the purpose of the investigation was to determine hepatic function in relation to diabetes, eleven of these were excluded. Seven had definite manifestations of injury to the liver, the clinical diagnosis being catarrhal jaundice, carcinoma of the pancreas, adenoma of the liver, portal cirrhosis, alcoholic cirrhosis, metastatic carcinoma of the lungs and liver and carcinoma of the liver, respectively. Three others had a severe grade of nephritis and another syphilis.

The twenty-eight patients selected from group C afforded no clinical manifestations of hepatic dysfunction, and it was impossible to determine any complicating factor besides diabetes, which could in any way influence the tests for hepatic function. These patients apparently furnish

an index of hepatic function in patients well treated for diabetes mellitus. They were found to be older, to be only slightly heavier and to have a history of longer duration than the members of group A. The average value of the blood sugar during fasting was higher, the insulin requirement practically identical and the cholesterol readings somewhat lower.

If 0.3 mg is taken as the high normal for the van den Bergh reading, it is less delicate than the bromsulphalein test. It exceeded 0.3 mg in nine cases. As noted by other investigators, secondary anemia tends to produce a hypobilirubinemia.

TABLE 4—Summary of Data on Groups A, B, C-1 and C-2

	Group A	Group B	Group C 1	Group C 2
Patients	48	13	11	28
Sexes	25 M, 23 F	7 M, 6 F	5 M, 6 F	19 M, 9 F
Average age, yr	49.5	50.1	52.2	52.2
Average weight, lb	131.8 (59.8 Kg)	152.7 (69.3 Kg)	135.1 (61.25 Kg)	133 (60.3 Kg)
Average duration of illness, yr	2.7	3.3	1.2	3.3
Average insulin units	33.3	41.5	25.7	31.5
Average blood dextrose, mg	142.4	147.3	124.1	159.7
Average urea nitrogen, mg	14.8	14.5	27	14.2
Average cholesterol, mg	188.2	183.2	157	173.3
Average carbon dioxide	51.4	51.5	49.7	51.8
Average hemoglobin, Gm	13.5	13.7	12.6	13.3
Wassermann reactions	All negative	All negative	10 negative, 1 positive	All negative
Average urobilinogen dilution	1:14	1:11	1:105	1:28
Average icterus index	5.7	5.2	35.5	6
Results, qualitative van den Bergh test	5 faint delay 43 negative	6 faint delay 7 negative	2 biphasic 2 immediate 6 negative	13 faint delay 16 negative
Average quantitative van den Bergh test	0.17	0.20	4-1	0.30
Average bromsulphalein retention, %	0	0-3	29.8	5.4

In group A, liver function tests all gave normal results.

In group B, liver function tests all gave normal results, except possibly nine cases with from 0 to 3 per cent bromsulphalein retention and two cases with van den Bergh results of 0.4 mg and two with 0.5 mg.

In group C 1, liver function tests (one or more) gave definitely positive results. These cases all presented demonstrable complications (seven clinical disease of liver, three nephritis, and one syphilis).

In group C 2, liver function tests (one or more) gave definitely positive results. These cases presented no demonstrable complications or any clinical manifestations of disease of the liver. All were standardized.

The icterus index was found to be subject to greater personal error than the van den Bergh test. It was of value only when the serum was free from hemolysis, and the results more nearly paralleled the van den Bergh readings when the phosphate buffer was used for dilution. It was greater than 6 in eight cases.

The urobilinogen test was found to be convenient, simple, practically free from personal error, nontime-consuming and of no annoyance to the patient. It gave a result exceeding 1:20 in ten cases, and 1:10 in eighteen cases.

The bromsulphalein test usually showed some retention. It was free from prolonged discomfort or hazard and easily performed. It was found to give definitely positive results in twenty-one cases, and questionably positive results (from 0 to 3 per cent) in three cases in which

the urobilinogen and quantitative van den Bergh tests suggested hepatic dysfunction. The four others presented no retention of dye, but all showed an increase of urobilinogen. Probably in one of these cases there was also an abnormal reading for serum bilirubin, but in the remainder the results were within the normal range.

Apparently in the case of standardized diabetic patients, the bromsulphalein test will be found to give a positive result most frequently. In the study of hepatic function, it seems advisable to conduct a series of complementary tests for the estimation of this function and to correlate carefully the clinical data before attempting their interpretation.

The cholesterol readings exceeded 170 mg in twelve cases, but it was impossible to explain the significance of this elevation as related to hepatic function.

The data for groups A, B, C-1 and C-2 are found in table 4.

CONCLUSIONS

1. Clinical and laboratory studies apparently indicate that hepatic dysfunction is a frequent occurrence in diabetes mellitus. Of the cases studied, 7 per cent showed both clinical and laboratory evidence of hepatic dysfunction, 28 per cent furnished only laboratory data, 48 per cent were without any abnormal indications and an additional 13 per cent gave only minimal or doubtful readings.

2. The older the patient and the longer the diabetes mellitus remains uncontrolled, the more frequently hepatic dysfunction becomes demonstrable.

3. Even though the bromsulphalein test was found to yield positive results most frequently, it seems advisable to conduct a series of complementary tests.

4. The study of these cases over an extended period of time created the impression that the modern diabetic regimen materially aids in improving hepatic function and in conjunction with proper preoperative and postoperative treatment permits even diabetic patients with clinical manifestations of hepatic dysfunction to undergo major surgical operations with comparative safety. This study also showed that any patient in whom hepatic dysfunction is demonstrated might advantageously be placed on a prescription diet and a careful search instituted for evidence of latent or potential diabetes.

INSUFFLATION OF COMPRESSED AIR IN THE TREATMENT FOR PNEUMONIA *

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CHICAGO

In a previous study¹ it was noted that in the dog an increased intra-pulmonic pressure would result in interstitial emphysema, acute pneumothorax, pneumoperitoneum and air embolism. It was found that air injected intrabronchially under increased pressure had little or no effect if a good outlet for it was supplied. If, on the other hand, there was an insufficient outlet or a complete blocking of the outflow of air, the lung expanded when the intrabronchial pressure was raised between 20 and 35 mm of mercury. When the pressure reached a point between 60 and 100 mm of mercury, invariably, the dogs showed the syndrome of interstitial emphysema, pneumothorax, pneumoperitoneum and air embolism. These results were obtained in dogs with normal and also with pneumonic lungs.

We have repeatedly noticed that the pulmonary vessels can be emptied easily by increasing the alveolar pressure. In fact, after severing the heart from its connections with the pulmonary vessel, we have been able to wash out all the blood from the pulmonary vessels by allowing the inflow of compressed air into the lung. The pressure at which this air was blown into the lungs was just high enough to distend them to their optimum volume, but not to distend them to the point of maximum drumlike distention. Under such conditions after the air was allowed to flow for a few minutes, it was noticed that blood oozed slowly from the severed ends of the pulmonary vessels, and eventually only air came through. When this point was reached, a surface stereomicroscopic study of the lung showed a complete replacement of the blood by air in the smaller as well as in the larger vessels. By filling the alveoli with a fixing solution and then blowing air under these conditions we have been able to force this fluid from the alveoli into the pulmonary circulation without any apparent gross or microscopic injury to the alveolar wall.

AIR EMBOLISM

The phenomenon of air embolism is probably more frequent than is generally supposed. We have repeatedly noticed air finding its way

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¹ From the Department of Surgery, College of Medicine, University of Illinois

1 Joannides, M., and Tsoulos, G. Experimental Production of Interstitial Emphysema and Air Embolism, *Arch Surg* **21** 333 (Aug) 1930

into the pulmonary vessels of the frog when the animal struggled sufficiently during the normal expansion of the lung to cause an increased intrapulmonic pressure. Undoubtedly the reason why the phenomenon is not recognized clinically is that small amounts of air in the circulation are well borne, but large amounts, injected over a short period of time, reaching the heart and finally some vital area of the brain, cause shock or transitory hemiplegia. The so-called pleural shock produced during the induction of artificial pneumothorax has been definitely shown by Van Allen and his associates to be related to air embolism.²

When a large amount of air reaches the heart, it comes in contact with the blood, which is a colloidal solution and has a tendency to emulsify much in the same manner as soap, so with each cardiac contraction the blood is broken up into smaller and smaller air bubbles and the animal dies of anoxemia and asphyxia. Some of this emulsified blood finds its way into the general circulation and there it can be identified as air bubbles all along the course of the vessels. A good method for determining the presence of air in the circulation is to insert a needle of a wide gage into the vein, and, as the blood is sucked into a syringe, air bubbles if present in the vein, will be visible in the syringe. A more accurate method of searching for bubbles in the smaller vessels and capillaries is by means of a capillary microscope.

Since it is easy to squeeze fluids into the pulmonary circulation under normal conditions, we decided that it might be of value to try this method in the treatment of pneumonia. In this disease it is evident that the exudates that are produced in the alveolar wall follow the path of least resistance and drain into the alveolar sac.³ In pneumonia, regardless of the etiology or the severity we found that the steps in the development and course of the disease are no different than those in acute inflammation elsewhere in the body. The differences presented are those due to the peculiar structure of the lung.⁴

* CARDIOCIRCULATORY COMPENSATION IN PNEUMONIA

The lung is a very vascular organ, and the flow of the blood in the pulmonary vessels depends, among other things, on the intermittent

2 Van Allen, C. M., Hrdina, L. S., and Clark, J. Air Embolism from Pulmonary Vein. Clinical and Experimental Study. *Arch. Surg.* **19**: 567 (Oct.) 1929.

3 Joannides, M., and Steinman, F. The Mechanism of Pneumonia, *Arch. Int. Med.* **47**: 24 (Jan.) 1931.

4 A detailed discussion appears in the article by M. Joannides and F. Steinman (footnote 3).

expansion and contraction of the lung tissue. When the lung becomes immobilized by external compression or internal drowning with exudate, it becomes fairly solid and loses its elasticity, so that little or no air enters and leaves the lung during inspiration and expiration. This immobilization of the lung has a definite effect on the circulation and the oxygen carrying capacity of the blood. The circulation becomes impeded, the heart suffers from overwork and asphyxial changes, so that sooner or later the patient collapses because of the cardiac and circulatory decompensation. In other words, in pneumonia, the patient needs a proper cardiocirculatory compensation, a proper supply of oxygen and the elimination of waste products accumulating in the blood stream as a result of asphyxia.

We noticed experimentally that the circulation in normal dogs suffers definite changes coincident with the production of an open pneumothorax. Under normal conditions the record of blood pressure in a dog, obtained by direct connection with the femoral artery, shows definite respiratory waves. These waves promptly disappear with the production of open pneumothorax, and if artificial respiration is not instituted, the amplitude of the wave becomes gradually shorter, eventually reaching a pulse pressure of almost zero. At this point frequently (for some reason as yet unexplainable) the blood coagulates in the cannula. If the animal is let alone, the systolic pressure takes a sudden drop much in the manner of the blood pressure in an animal dying from an overdose of chloroform. The heart at this point also shows a definite and quite constant bradycardia before it finally stops beating. If such an animal is treated by means of artificial respiration at any stage of the cardiocirculatory collapse, the normal respiratory waves are again apparent in the record of the blood pressure, and the animal may be kept alive for as long as it is desired. In the late stages of cardiac collapse, in which asphyxial bradycardia occurs just before the heart finally stops beating, it is necessary that artificial respiration be established. When artificial respiration is instituted, it is quite necessary that the flow of compressed air in the lungs be intermittent, and there should be a sufficient blocking of the outflow of air in the system of tubing to increase the intrapulmonic pressure to a point between 20 and 35 mm of mercury for the dog. The blocking of the outflow must be complete and just long enough so that the desired pressure is obtained. The expanded lung thus fills up the thoracic cavity, and at the same time causes a slight bulging in the wall of the chest at the costal margin and in the anterior abdominal wall. For measuring intrapulmonic pressure we have used a diaphragm

air pressure indicator furnished by Dr. A. Littig,⁵ chief anesthetist of the Illinois Research and Educational Hospitals

It is obvious to those who do much work under artificial respiration that it is not necessary to use either pure oxygen or oxygen mixed with carbon dioxide. Such a provision, at least in the experimental animal, has been found unnecessary and expensive. Ordinary compressed air has a sufficient amount of oxygen to take care of the asphyxia. The increased pressure, on the other hand, under proper management, allows for sufficient expansion and contraction of the lung to reinforce the heart and the circulation.

In pneumonia, a disease in which consolidation results from the drowning of the alveoli and the edema of the interalveolar wall, the use of positive pressure in artificial respiration theoretically would be of definite benefit. The increased intrapulmonic pressure (from 20 to 35 mm. of mercury) will help to stretch and contract the interalveolar wall. It will also aid in squeezing some of the exudate from this wall into the circulation because the interalveolar pressure is now higher than the pressure of the blood in the pulmonary vessels. Moreover, some of the exudate in the alveolar space will find its way into the circulation. Finally, the lung will get sufficient oxygenation to take care of the anoxemia and asphyxia. We tried this method in dogs when the animal was dying from pneumonia. It was noticed that an animal so weak physically that one could barely see the respiratory movements, and to all appearances almost dead, began to breathe normally after artificial respiration was established for from one to five minutes, and continued to do so for a period of from ten minutes to an hour before it again showed signs of collapse. The rate of obstructed outflow was from 20 to 30 times per minute, and the intrapulmonic pressure varied from 20 to 35 mm. at the peak and from 5 to 10 mm. of mercury when the outflow of air was completely open.

The anatomic changes that occurred in the pneumonic lung are of interest. When the intra-alveolar pressure was increased in the dog to a point between 20 to 35 mm. of mercury the liver-like, dark-colored consolidated lung began to expand and to present a crepitating appearance and the color became pinkish red, but the vessels still stood out prominently. When the lung was allowed to collapse it was no longer solid, but showed crepitation and a less purple color. Microscopically, this lung showed alveolation just like that in the normal lung, but definite changes in the alveolar surface and in the wall still persisted.

5 Littig, A. Measurement of Positive Pressure Used in Gas Anesthesia. Wisconsin M. J. 28:217 (May) 1929, Anesth. & Analg. 9:82 (March-April) 1930.

TECHNIC

A brief description of the technic in the administration of the compressed air may be of value

The compressed air obtained from a tank is connected to an air-tight mask by means of rubber tubing. This tubing, by the use of T or Y glass or metal tubings, provides for an outlet and also for the connection to the Littig manometer.⁶ One provision is essential, namely, that the diameter of the tubing at the outlet of air should be the same, or even greater, than the diameter of the tubing attached to the mask. For the mask, half-inch tubing is best. For the attachment to the Littig manometer, a tubing one-fourth inch in diameter is sufficient. The compressed air is now allowed to run into the lungs of the animal, and the pressure is adjusted to a point of 5 or 10 mm of mercury with the outflow completely open. The outflow is now completely closed with the finger until the animal shows a bulge in the anterior abdominal level and at the costal margin. This occurs coincidentally with the rise of the intrapulmonic air pressure to from 20 to 35 mm of mercury. The outflow is now released, and one sees a collapse of the thoracic and abdominal wall. The length of complete closure in the outflow until expansion of the lung takes place varies with the initial pressure. When this initial pressure is high, the expansion occurs faster, and the intrapulmonic pressure varies from 25 to 35 mm of mercury. Care must be taken not to increase the pressure too long or too high, because the syndrome of interstitial emphysema results.¹ At times the stomach may become greatly distended with air during this treatment. Such distention is distressing to the patient, and it interferes with the respiratory excursion of the diaphragm. It is best treated by the passage of a stomach tube to a point beyond the cardia in which obstruction occurs.⁷

At the present time these studies have been limited to the dog. The exact pressure at which the human lung expands is now being measured. A clinical trial will be made as soon as the optimum pressure is obtained.

SUMMARY

1 Increased intra-alveolar pressure, when excessive, produces interstitial and mediastinal emphysema, pneumothorax, pneumoperitoneum and air embolism.

2 Increased intra-alveolar pressure causes emptying of the pulmonary vessels when severed from the heart.

3 In pneumonia, the alveoli are drowned with exudate coming from the interalveolar wall and the alveolar surface.

4 Cardiocirculatory collapse follows the consolidation and immobilization of the lung, which causes stasis because of the absence of intermittent expansion and contraction.

⁶ Littig (footnote 5, first reference)

⁷ Joannides, M. Surgery of the Lung. Care of the Stump in Pneumectomy and in Lobectomy. *Arch Surg* **17** 91 (July) 1928. The Relation of the Hiatus Esophageus of the Diaphragm to the Stomach, *Arch Int Med* **43** 61 (Jan) 1929.

5 The heart and the circulation improved when intermittent artificial respiration was instituted in pneumonic lungs as well as in open pneumothorax

6 A pressure of from 20 to 35 mm of mercury is sufficient to cause complete expansion of the normal as well as of the pathologic lung

7 Compressed air serves the purpose of artificial respiration safely and inexpensively. It is not necessary to use pure oxygen or a combination of oxygen and carbon dioxide

8 The outflow of the air is important, because it regulates the degree of pressure in the lung, the amount of air blown in, the degree of lung expansion and the prevention of the interstitial emphysema syndrome

9 Pneumonic, consolidated, dark-colored lungs when subjected to increased intrapulmonic air pressure either inside or outside of the body became crepitating and pinkish red again

THE COMPARATIVE CHANGES IN GASTRIC ACIDITY AND URINARY REACTION AFTER THE INJECTION OF HISTAMINE¹

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AND

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In a previous communication,¹ we discussed the advantages of a test combining analysis of gastric contents with estimation of urinary acidity as a method of obtaining more controlled results in the determination of gastric acidity

It has been known that persons having relatively normal gastric secretion are prone to have less acid urine after meals, a phenomenon commonly referred to as the "alkaline tide" On the other hand, a relative fixation of the urinary reaction has been shown to exist in patients with true achlorhydria These observations were recently confirmed by Hubbard and his co-workers^{1a} and by Baehr,² Davis³ and others

We decided to employ histamine as the gastric stimulant in our studies Histamine has been recognized as the most reliable gastric stimulant for hydrochloric acid by numerous workers, particularly Andresen⁴ and Gompertz and Vorhaus⁵ Ackman⁶ was particularly interested in studying the relationship between the gastric acidity and the hydrogen ion concentration of the urine after the injection of histamine It occurred to us to employ this principle of the relationship between the gastric acidity and the true urinary acidity (p_H) in a clinical secretory test with histamine as the gastric stimulant

METHOD OF PROCEDURE

The patient was requested to urinate at 6 30 a m, emptying the bladder as completely as possible This was done again at 8 30 a m, and the hydrogen ion concentration (p_H) of the second specimen was determined immediately

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1 Matzner, M J, and Gray, I A Critique of Present Methods for the Study of Gastric Acidity, Arch Int Med **47** 58 (Jan) 1931

1a Hubbard, R S, Munford, S A, and Allen, E G Am J Physiol **68** 207, 1924

2 Baehr, G Bull New York Acad Med **3** 419, 1927

3 Davis, D T Brit J Exper Path **10** 1 (Feb) 1929

4 Andresen, A F R Tr Am Gastro-Enterol A, 1926, p 53

5 Gompertz, L M, and Vorhaus, M G J Lab & Clin Med **11** 14 (Oct) 1925

6 Ackman, F D Canad M A J **15** 1099, 1925

A Rehfuß tube was passed about 9 a. m., and the contents of the fasting stomach were extracted. The stomach was lavaged with water until a clear return was obtained. Immediately thereafter from 0.25 to 0.5 mg. of histamine was injected subcutaneously. Gastric extractions were made every hour over a period of from three to five hours. The patient was instructed to empty the bladder completely at each urination. The gastric specimens were quantitatively analyzed for free and total acidity.

The hydrogen ion concentration of the urine (p_H) was immediately determined with the Hellige comparator.⁷ This method is extremely simple and in contradistinction to other methods lends itself readily to clinical use. The determination can be made in a few minutes.

Care was exercised in this study to prevent errors from variations in the respiratory exchange. The patient was kept as nearly at absolute rest as possible throughout the test. We essentially adopted the practice of Hubbard, Munford and Allen,¹ of accepting as evidence of an alkaline tide a change of p_H of 1 in one specimen or of 0.5 p_H in two specimens. These authors found that if this criterion was accepted, the results of the urinary test failed to agree with the results of the fractional gastric analysis in about 20 per cent of all the determinations carried out.

RESULTS

We employed this method in a study of twenty-five patients. Not more than 50 per cent of our patients who had free hydrochloric acid in the gastric extractions after the injection of histamine had a definite urinary alkaline tide. Our results may be classified as follows:

Group 1. Patients with free hydrochloric acid and definite urinary alkaline tide, 6. In this group, after the injection of histamine, free hydrochloric acid was demonstrated in the extracted gastric specimens, while the development of a definite alkaline tide was shown by the urinary tests.

Group 2. Patients with free hydrochloric acid and no urinary alkaline tide, 6. In this group, free hydrochloric acid was demonstrated in the extracted gastric specimens. However, in contradistinction to the patients of group 1, these patients did not show a definite urinary alkaline tide.

Group 3. Patients with no free hydrochloric acid and no urinary alkaline tide, 12. In this group, free hydrochloric acid was not demonstrated in the extracted gastric specimens after the injection of histamine. A simultaneous study of the urine showed a relative fixation of the urinary reaction (no alkaline tide).

Group 4. Patients with no free hydrochloric acid and a definite alkaline tide, 1. This patient, J. C., a man, aged 58, was admitted to the gastro-intestinal service of Dr. Irving Gray, with a history of anorexia, gradual loss of weight and progressive dysphagia. The "combined test" showed the following discrepancy: a definite urinary alkaline tide but no free hydrochloric acid in the extracted specimens.

⁷ The apparatus can be obtained from Eimer and Amend, New York.

In seeking an explanation for the discrepancy between the gastric analysis and the urinary alkaline tide, it was surmised that the Rehfuß tube might be coiled up in the esophagus, owing to an obstruction at its lower end. If this were so, our analyses were esophageal rather than gastric. Immediate fluoroscopic examination with the Rehfuß tube in situ was done. These examinations definitely demonstrated the Rehfuß tube coiled up in the esophagus. The discrepancy between the gastric analysis and the urinary alkaline tide was thus readily explained.

TABLE 1—Results of "Combined Test" in Group 2

Name	Clinical Diagnosis	Maximum Gastric Acidity		pH of Urine			
		Free HCl	Total Acidity	9 30 a m pH 5	10 10 a m pH 5	11 a m pH 5	12 30 p m pH 4.8
J L	Neurosis	60	70				
K B	Duodenal ulcer	18	24	9 a m pH 4.8	9 55 a m pH 5	11 05 a m pH 5	12 m pH 5
A F	Duodenal ulcer	70	79	9 30 a m pH 5	10 30 a m pH 5	11 15 a m pH 5	2 p m pH 5.2
J S	Neurosis	11	18	9 40 a m pH 5	10 30 a m pH 5	11 45 a m pH 5.2	2 p m pH 5.2
B D	Duodenal ulcer	73	78	9 15 a m pH 5	10 15 a m pH 5	11 a m pH 5	12 30 p m pH 4.8
C D	Neurosis	30	34	9 15 a m pH 7.2	10 15 a m pH 7.2	11 25 a m pH 7.4	12 30 p m pH 7

TABLE 2—Results of "Combined Test" in the Case of J C

Time	Gastric Analysis		Urinary pH
	Free HCl	Total Acidity	
9 30 a m	0	2	5.2
10 00 a m	0	4	5.2
10 30 a m	0	2	6.8
11 30 a m	0	4	6.8

COMMENT

Not more than 50 per cent of the patients in whose gastric extractions we were able to demonstrate free hydrochloric acid after the subcutaneous injection of histamine had a definite urinary alkaline tide. Several considerations suggest themselves to explain this apparent discrepancy. First, it is known that histamine causes an increased secretion of bile and of alkaline intestinal juices. This simultaneous alkaline intestinal secretion might be sufficient at times to offset or to neutralize the effect of the secretion of hydrochloric acid into the stomach. Second, while the stimulus of histamine for gastric secretion is maximum, it is usually not of long duration. The total quantity of

hydrochloric acid secreted may thus not always be sufficient to cause an appreciable change in the urinary reaction

Kauders, Porges and Essen⁸ drew attention to a group of patients with hypersecretion (Reichmann's disease), who in their opinion are less apt to have an alkaline tide after a test meal, because their gastric acidity values are practically maximum throughout the day and less likely to rise appreciably after a test meal

Hubbard⁹ recently emphasized that the investigation of the urinary alkaline tide should be done several hours after the patient's waking. The liberation of the carbon dioxide stored up during the night might be sufficient in itself to exert an influence on the urinary reaction. We have taken this precaution in our studies

We gained the impression from Ackman's⁶ studies that his patients also received breakfast on the morning that histamine was injected. Of course if that were so, a satisfactory explanation would be at hand for the greater percentage of urinary alkaline tides reported in his comprehensive investigation of the effect of histamine on the urinary alkaline tide

The fact that not more than 50 per cent of our patients in whose gastric extractions free hydrochloric acid was demonstrated after the subcutaneous injection of histamine had a definite urinary alkaline tide led us to abandon histamine as the gastric stimulant in the "combined test." We are employing bouillon (one Steero cube in a cup of warm water) at present, and our results will be published in a subsequent paper

SUMMARY

1 The advantages of a test combining gastric analysis and estimation of urinary acidity (alkaline tide) are discussed

2 Histamine was employed as the gastric stimulant

3 Not more than 50 per cent of the patients in whose gastric extractions free hydrochloric acid could be demonstrated after the injection of histamine had a definite urinary alkaline tide

4 The use of histamine as the gastric stimulant in studies of the urinary alkaline tide has been discontinued. More favorable experiences with Steero bouillon as the gastric stimulant in our studies of the urinary alkaline tide will be reported in a subsequent paper

⁸ Kauders, F., Porges, O., and Essen, H. *Deutsche med. Wchnschr.* **47** 1415 (Nov. 24) 1921

⁹ Hubbard, R. S. *J. Biol. Chem.* **84** 191 (Oct.) 1929

NORMAL VARIATIONS IN ERYTHROCYTE AND HEMOGLOBIN VALUES IN WOMEN *

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Red blood cell counts and hemoglobin determinations have been thought by some investigators to fluctuate but little in an individual during the day and by others to show large variations. As it is important to know whether isolated counts should be considered in relation to the time of day of the count and the activity of the person, this study was initiated to determine the variations of erythrocytes and hemoglobin values during short periods of time. It was found that with accurate technic, the red blood corpuscles and the hemoglobin determinations remain remarkably constant during the day, and that there are no significant changes due to rest, moderate activity or food. Real differences may occur, however, between counts for separate days and between averages for longer periods of time.

TOTAL COUNTS OF ERYTHROCYTES

Technic—The inaccuracy that may attend blood counting has invalidated many experiments in which this technic has been used. Krumbhaar¹ (1928) stated that there are sixteen sources of error in making total counts which "if all were cumulative might easily produce a total error of more than 40 per cent without any one item passing a reasonable 'limit of error'". In European hematologic work simple statistical methods have been used to aid in testing the accuracy of the technician and to determine the significance of results, but in this country only a few of the more recent papers have treated data in this way (table 1)

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¹ Krumbhaar, E. B., in Cowdry, E. V. *Special Cytology*, New York, Paul B. Hoeber, Inc., 1928, p. 284

Because it seemed necessary to have some definite procedure by which the accuracy of the technician could be tested, the following method has been used throughout this investigation. First each operator counted the cells in 10 or 20 drops from the same pipet until the coefficient of

TABLE 1—*Determinations of Error Inherent in the Technique*

Author	Date	Coefficient of Variation, per Cent	Method
Vierordt, K. <i>Arch f physiol Heilk</i> 11 868, 1852	1852	2.36	9 series, 30 counts different days
Welcher, H. <i>Prag Vrtljschr f d prakt Heilk</i> , 1854, p. 25	1854	1.89	2 series, 14 counts
Reinert, E. <i>Die Zahlung der Blutkorperchen und deren Bedeutung fur diagnose und Therapie</i> , Leipzig, F. C. W. Vogel	1891	2.97 3.00	5 drops from the same pipet sufficiently accurate value
Burker, K. <i>Munchen med Wchnschr</i> 59 89, 1912	1912	1.8	7 consecutive days, 4 times 80 squares each day
Jorgensen, G. <i>Ugesk f læger</i> 75 1733, 1913	1913	2.5	
Terhola, L. <i>Arch r Gynak</i> 103 115, 1914	1914	2.9 3.4	For single determinations 9 series, 41 counts
Bing, H. I. <i>Ugesk f læger</i> 81 1483, 1919	1919	2.3	
Craandyk, M. M. <i>Folia haemat</i> 23 11, 1918-1919	1918-1919	3.1, 3.4	6 days, 7 duplicate counts
Hansen, K. M. <i>Ugesk f læger</i> 81 1281, 1919	1919	1.73, 2.17	
Bierring, K. <i>Ugesk f læger</i> 82 1445, 1920	1920	3.2	
Feucht, B. <i>Arch f d ges Physiol</i> 187 139, 1921	1921	1.48	30 counts within 5 days
Emerson, C. P. <i>Clinical Diagnosis</i> , Philadelphia, J. B. Lippincott Company	1921	estimated 2.0 4.0	In counting includes physiologic variations
Mayers, L. H. <i>Arch Int Med</i> 30 478 (Oct.) 1922	1922	0.2 4.75	5 counts in 7 hours 7 consecutive days
Rud, E. J. <i>Acta med Scandinav</i> 57 142, 1922-1923	1922-1923	1.18 to 2.63	10 determinations, 3 series
Brandt, T. <i>Folia haemat</i> 32 177, 1926	1926	2.3	10 determinations
Laseh and Billich. <i>Ztschr f d ges exper Med</i> 48 651, 1925-1926	1926	2.6	6 drops same mixture
Osgood, E. E. <i>Arch Int Med</i> 37 685 (May) 1926	1926	3	Maximum experimental error
Ponder and Millar. <i>Quart J Exper Physiol</i> 19 145, 1928	1928	5	Maximum experimental error

variation was at least less than 3 per cent. Then 10 or 20 drops from each of two pipets from the same drop of blood were counted until the difference between the two means was considered insignificant according to its probable error. Previously it has been thought that successive drops from the same pipet would not have the same cell content because the air bubbles present would have influenced the distribution of the

cells (Komocki,² 1924) In this work little difference was found between successive drops when accurate manipulation has been attained Successful results were obtained only after repeated practice periods, the length of time depending on the person

For the definition of terms and for the formulas and their use, reference may be made to any of the standard textbooks on statistical methods, but it seems desirable to specify the few used in this work

a = arithmetical mean or average

d = deviation of an item from the mean

n = number of items

standard deviation = $\sqrt{\frac{\text{sum of } d^2}{n}} = \sigma$

coefficient of variation = $\frac{\text{standard deviation}}{\text{mean}} \times 100$

probable error of mean = $\frac{\text{small } n}{0.6745\sigma} \quad \frac{\text{large } n}{0.6745\sigma}$
 $\frac{0.6745\sigma}{\sqrt{n-1}} \quad \frac{0.6745\sigma}{\sqrt{n}}$

probable error of standard deviation = $\frac{0.6745\sigma}{\sqrt{2(n-1)}} \quad \frac{0.6745\sigma}{\sqrt{2n}}$

probable error of coefficient of variation = $\frac{0.6745 \text{ c.v.}}{\sqrt{2(n-1)}} \quad \frac{0.6745 \text{ c.v.}}{\sqrt{2n}}$

The value of the method presented in table 2 as a measure for testing the accuracy of the technician either in the training of new workers or in the verifying of the exactness of old workers who have had long or short interruptions can be seen by examining the results obtained by technicians A and D in table 3 Technician D had done no blood counting until two weeks previous to the series reported here, and within that time her efficiency increased steadily As her operations became more exact, the distribution of cells became more even and the coefficient of variation correspondingly less This procedure may be applied to work involving total white counts and hemoglobin determinations

In summary, the following statements may be made concerning the advantages of applying simple statistical methods to the appraisal of technical efficiency in blood counting

1 The coefficient of variation for the cells counted from one pipet has a definite meaning It is the measure of the distribution of the cells after the pipet has been filled In red counts a coefficient of from

² Komocki, W Ueber die Zahl der roten Blutkörperchen bei gesunden erwachsenen Menschen Virchows Arch f path Anat **253** 386, 1924

TABLE 2—Method of Determination of the Coefficients of Variation and of the Significance of the Difference Between Two Pipets (Ten Counts from Each)

Pipet D3			
	d	d ²	
1	431 +8	64	$\sigma = \sqrt{\frac{\text{sum of } d^2}{n}} = \sqrt{\frac{22}{10}} = 0.25 = 17$
2	425 +2	4	
3	415 -8	64	Probable error of $\sigma = \frac{0.6745 \sigma}{\sqrt{n-1}} = \frac{0.6745 (17)}{3} = 10.6$
4	420 -3	9	
5	427 +4	16	Probable error of $\sigma = \frac{0.6745 \sigma}{\sqrt{2(n-1)}} = \frac{0.6745 (17)}{4.2} = 0.71$
6	427 +4	16	
7	425 +2	4	Probable error of c v = $\frac{0.6745 \text{ c v}}{\sqrt{2(n-1)}} = \frac{0.6745 (11)}{4.2} = 0.176$
8	426 +3	9	
9	422 -1	1	
10	417 -6	36	
	+23 -18	223	
d' =	$\frac{+23 -18}{10} = \frac{5}{10} = 0.5$		

$$\begin{array}{rcl} \tau & = & 123 \pm 0.5 = 423.5 \pm 1.076 \\ \sigma & = & 4.7 \pm 0.754 \\ c.v. & = & 1.1\% \pm 0.2\% \end{array}$$

Number of cells in a cubie millimeter = $\times 10,000$

n	=	4,235,000	±	11,000
σ	=	47,000	±	8,000
c v	=	1.1%	±	0.2%

Pipet D4

n	=	4,223,000	±	12,000
σ	=	53,000	±	9,000
e v	=	1.3%	±	0.2%

Probable Error of the Difference Between Two Pipets

Probable error $(4,235 - 4,223) = \sqrt{11,000^2 + 12,000^2} = \sqrt{265,000,000} = 16,000$. The difference, 12,000, is less than its probable error, 16,000, and therefore it is not significant. "Unless a deviation is more than four times its probable error, there is no great reason for thinking it may not result from pure chance" (Gavett, G. I. *A First Course in Statistical Method*, New York, McGraw Hill, 1925, p. 183).

* In this table, 431, etc. = number of cells counted in 80 small squares $n = 10$ $d =$ deviation from assumed average $a' =$ assumed average $= 423$ $a =$ average or arithmetic mean $d' =$ deviation of average (a) from assumed average (a')

TABLE 3—Total Red Counts Cells per Cubic Millimeter (in Thousands),
Original Data Table 13

Teel man	Mean	Probable Error	Standard Deviation	Probable Error	Coefficient of Variation, per Cent	Probable Error, per Cent	No Drops from Pipet
C 1	4,639	± 17	110	± 12	2.3	± 0.3	20
2	4,273	± 15	99	± 11	2.3	± 0.3	20
3	4,476	± 15	100	± 11	2.2	± 0.2	20
A 1	4,355	± 26	170	± 18	3.9	± 0.4	20
2	4,286	± 19	125	± 14	2.9	± 0.3	20
3	4,130	± 14	90	± 10	2.2	± 0.2	20
4	4,038	± 18	116	± 13	2.9	± 0.3	20
5	4,354	± 13	83	± 9	1.9	± 0.2	20
6	4,256	± 10	74	± 7	1.7	± 0.2	20
D 1	4,770	± 18	82	± 13	1.7	± 0.3	10
2	4,679	± 13	63	± 9	1.3	± 0.2	12
3*	4,235	± 11	47	± 8	1.1	± 0.2	10
4*	4,223	± 12	53	± 9	1.3	± 0.2	10
F 1	3,928	-5	24	-4	0.6	-0.1	10
2	3,898	-4	17	-3	0.4	-0.1	10
3†	3,935	-2	8	-1	0.2	-0.03	10
4†	3,931	-2	7	-1	0.2	-0.03	10

^y D3 and D4 are two pinets from the same drop of blood

+ F3 and F4 are two pipets from the same drop of blood

3 to 4 per cent is an index of fairly good technic when 20 drops are counted from the same pipet, but less than 3 per cent should be attained. Adequate shaking of the pipet and even distribution of the cells in the counting chambers are the necessary prerequisites.

2 The size of the difference between the means of cells counted from two pipets from the same drop of blood is influenced by the taking and the diluting of the blood as well as by the distribution of the cells in the counting chambers. The means will approach each other as the technic becomes more accurate, and the difference should never be more than three times its probable error. The definiteness of this method, in which the technician checks himself, is to be preferred to one in which a second person counts from the same drop. It also excludes any consideration of the time of day or of physiologic variations between practice periods if counts are made on different days.

Method—Total counts were made with United States certified pipets and counting chambers on drops of blood from the finger tip. Hayem's fluid was the diluent. Two drops were counted from each pipet, or 160 small squares in all. Most of the data were obtained from women at half hour or hour intervals during eight hour periods on different days between the menses. All were in good health, although both the blood counts and hemoglobin determinations were low when compared with the normal standards. The investigation was purposely limited to a few people, because the aim was to study the daily variations of a small number of persons rather than scattered ones on many.

Observations—Variations in total counts from 8 a. m. through 3 p. m. were as follows (table 4, chart 1)

4 series	16 counts active (1, 2, 3, 10)
10 series	8 counts active (4-9, 11-14)
1 series	16 counts inactive 20
7 series	8 counts inactive (15-19, 21, 22)
<hr/>	
22 series	total

Results—Other data that had been accumulated earlier in the study were discarded because the errors were too large. All data, however, led to the conclusion that the red blood corpuscles remain almost constant in number during the day, and that the coefficient of variation for the day corresponds closely to the value previously obtained by the technician for the cells within the pipet. The accuracy of the technician should therefore always be known before conclusions are drawn concerning variations in total counts.

No difference is apparent between moderately active days and inactive ones for there is as much difference between two days of activity or two days of rest for the same person as between one of activity

and one of rest Activity has meant in these cases counting, writing and typewriting, and inactivity, rest in bed Table 4 and chart 1 show how closely these days resemble each other Although afternoon

TABLE 4—Total Red Blood Cell Counts (in Thousands)

8 a m Through 3 p m			Active (1 14)	Inactive (15 22)	Original Data Table 11					
Tech nician	Sub ject	Date	Mean	Probable Error	Standard Deviation	Probable Error	Coefficient of Probable Variation, per Cent	Error, per Cent	Num ber	
1	A	A	2/16/29	3,953	±19	109	±13	2.8	±0.3	16
2			2/17/29	4,005	±21	120	±15	3.0	±0.4	16
3			2/22/29	4,128	±24	137	±17	3.3	±0.4	16
4	D	B	7/27/29	4,281	±17	66	±12	1.5	±0.3	8
5			8/ 6/29	4,278	±10	38	±7	0.9	±0.2	8
6	D	D	12/ 1/29	4,131	±14	54	±10	1.3	±0.2	8
7			11/ 3/29	4,364	±5	21	±4	0.5	±0.1	8
8	F	D	5/11/30	4,243	±5	21	±4	0.5	±0.1	8
9			5/16/30	4,230	±4	15	±3	0.4	±0.1	8
10	C	E	2/16/29	4,596	±17	99	±12	2.2	±0.3	16
11	F	G	2/16/30	4,603	±21	81	±15	1.8	±0.3	8
12			3/ 2/30	4,510	±16	62	±11	1.4	±0.3	8
13			3/ 9/30	4,405	±15	57	±10	1.3	±0.2	8
14			5/11/30	4,543	±11	41	±7	0.9	±0.2	8
15	A	B	5/21/29	4,380	±14	53	±10	1.2	±0.2	8
16			5/27/29	4,491	±22	84	±15	1.9	±0.3	8
17	D	B	7/22/29	4,295	±23	90	±16	2.1	±0.4	8
18			7/28/29	4,255	±16	60	±11	1.4	±0.3	8
19			8/ 1/29	4,248	±7	28	±5	0.7	±0.1	8
20	A	E	5/ 5/29	4,213	±15	84	±10	2.0	±0.2	16
21			6/ 4/29	4,123	±20	76	±14	1.8	±0.3	8
22			6/ 5/29	4,175	±24	94	±17	2.3	±0.4	8
4 p m Through 11 p m			Active (27 32, 34 37)	Inactive (23 26, 33)						
23	D	B	7/23/29	4,236	±17	66	±12	1.6	±0.3	8
24			7/26/29	4,205	±13	49	±9	1.2	±0.2	8
25			7/31/29	4,223	±4	17	±3	0.4	±0.1	8
26			8/ 5/29	4,258	±7	26	±5	0.6	±0.1	8
27	F	B	5/ 3/30	4,100	±4	17	±3	0.4	±0.1	8
28			5/ 7/30	4,236	±5	18	±3	0.4	±0.1	8
29	D	D	10/31/29	4,131	±4	15	±3	0.4	±0.1	8
30			11/21/29	4,145	±19	73	±13	1.8	±0.3	8
31	F	D	5/ 7/30	4,034	±14	55	±10	1.4	±0.3	8
32			5/15/30	4,236	±5	18	±3	0.4	±0.1	8
33	B	E	6/16/29	3,745	±35	133	±24	3.5	±0.6	8
34	F	G	2/13/30	4,448	±14	54	±10	1.2	±0.2	8
35			4/ 6/30	4,195	±5	19	±3	0.5	±0.1	8
36			5/ 3/30	4,698	±7	28	±5	0.6	±0.1	8
37			5/ 4/30	4,521	±12	17	±9	1.0	±0.2	8
12 m Through 7 a m			Active (38)	Inactive (39 41)						
38	A	A	2/24/29	3,860	±20	113	±14	2.9	±0.4	16
39	D	B	7/30/29	4,245	±10	40	±7	0.9	±0.2	8
40			8/ 3/29	4,375	±9	35	±6	0.8	±0.1	8
41			8/ 4/29	4,287	±8	31	±7	0.7	±0.1	8

depressions appear in the composite curves for the active and inactive days taken separately and together, the decrease in the number of cells is so slight and the amount of data so small that the differences between the means for the morning and afternoon counts were found to be insignificant according to their probable errors

The differences between the morning and afternoon counts were as follows

8 a m through 11 a m

n = 44 11 series (1-7, 10-13)

a = 4,327,000 \pm 47,000

12 m through 3 p m

a = 4,261,000 \pm 49,000

difference = 66,000 \pm 68,000

8 a m through 11 a m

n = 76 19 series (1-7, 10-13, 15-22)

a = 4,312,000 \pm 37,000

12 m through 3 p m

a = 4,261,000 \pm 37,000

difference = 51,000 \pm 52,000

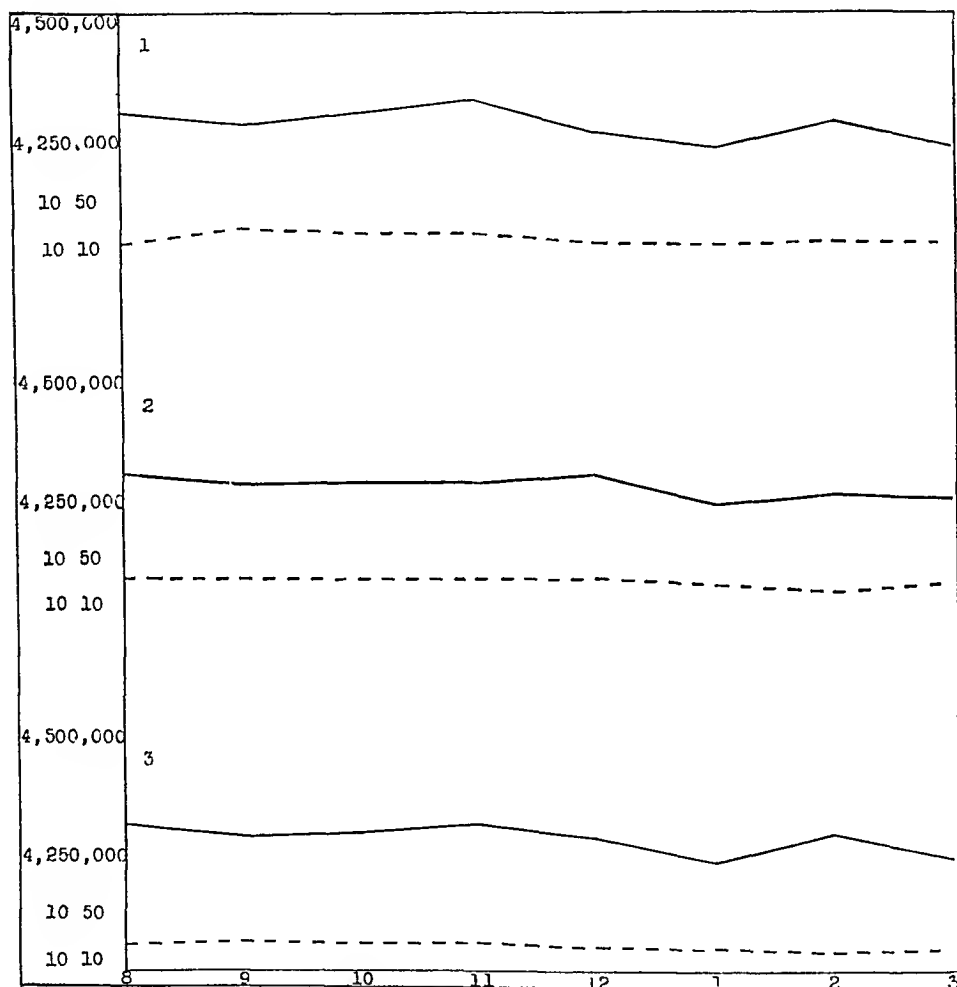


Chart 1—Total erythrocyte counts and hemoglobin determinations, 8 a m through 3 p m The continuous line indicates the curve for the total erythrocytes, the broken line, that for the hemoglobin, in grams per hundred cubic centimeters Curve 1 Erythrocytes composite curve, eleven series, active (1-7, 10-13) table 11 Hemoglobin, composite curve, eight series, active (1-8) table 12 Curve 2 Erythrocytes, composite curve, eight series, inactive (15-22) table 11 Hemoglobin, composite curve, five series inactive (9-13) table 12 Curve 3 Erythrocytes, composite curve, nineteen series (1-7, 10-13, 15-22) Hemoglobin, composite curve, thirteen series (1-13)

In six series no food was taken after breakfast (series 10, 15, 16, 20, 21, 22), and in the rest lunch was eaten between 12 and 2 o'clock. The average range (i.e., the difference between the highest and lowest items) for this period of the day for nineteen series (1-11, 15-22) is $251,000 \pm 18,000$, the maximum being 491,000 and the minimum, 60,000. These figures, which indicate the range of the counts, must also be interpreted according to the accuracy of the technic.

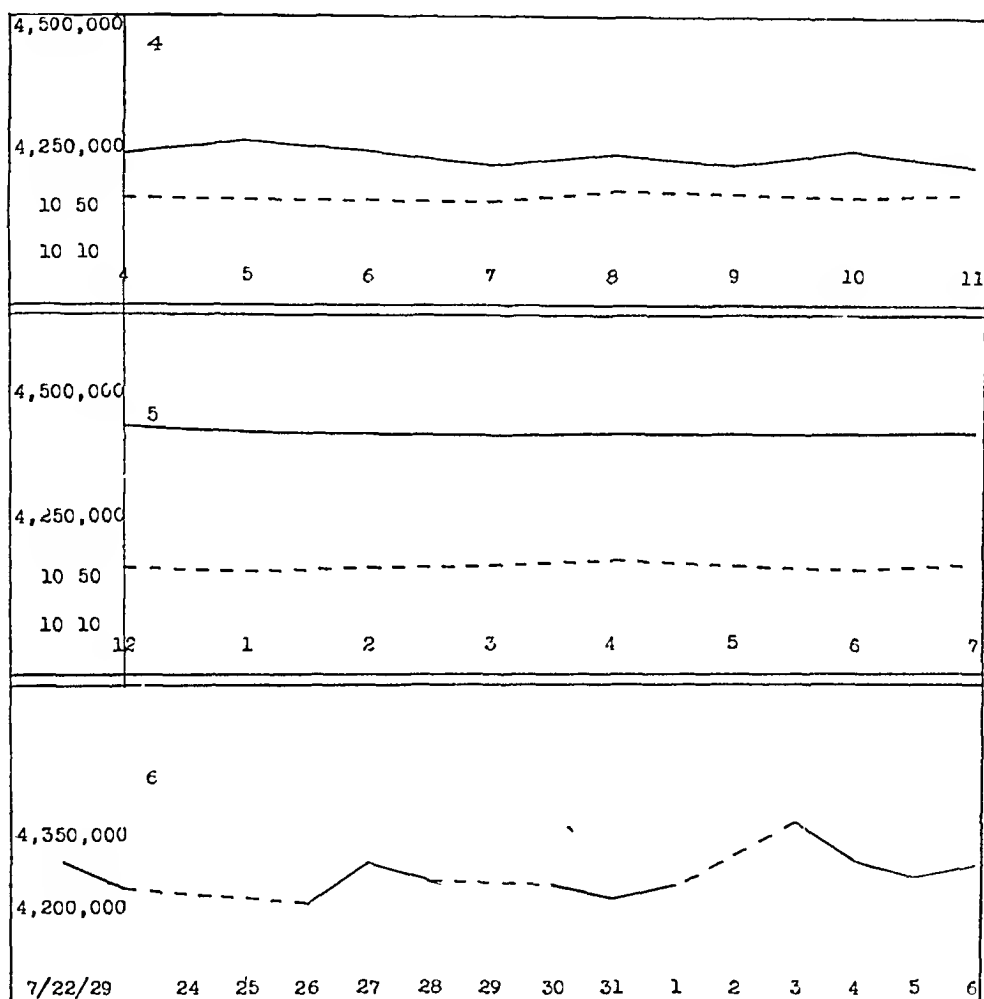


Chart 2—Total erythrocyte counts and hemoglobin determinations, 4 p. m. through 11 p. m. and 12 m. through 7 a. m. Total erythrocyte counts, twelve eight hour counts over a sixteen day period. The continuous line indicates the curve for the total erythrocytes, the broken line, that for the hemoglobin, in grams per hundred cubic centimeters. Curve 4 Erythrocytes, composite curve, fifteen series (23-37) table 11. Hemoglobin, composite curve, five series (14-18) table 12. Curve 5 Erythrocytes, composite curve, four series (38-41) table 11. Hemoglobin, composite curve, seven series (19-25) table 12. Curve 6 Twelve eight hour erythrocyte counts in a sixteen day period. Each point is the average for the day, table 5. The broken line in the curve indicates the omission of counts.

Observations—Variations in total counts from 4 p m through 11 p m (table 4, chart 2) were as follows

10 series 8 counts active (27-32, 34-37)

5 series 8 counts inactive (23-26, 33)

—
15 series total

Results—The data for this series of counts lead to the same conclusions as those just described for the 8 a m through 3 p m series. There were no fluctuations evident which were outside those that can be ascribed to technic. The depression in the afternoon which is seen in the curves for the day counts (8 a m and through 3 p m), but which cannot be proved as significant, seems to be continued in the evening as indicated by the lower values for these determinations. If the means for the 8 a m through 3 p m and the 4 p m through 11 p m counts for subjects, B, D and G are compared, singly and together, it is seen that in each case the one for the evening series is less than that for the day.

The differences between the day and evening counts were as follows

Subject	8 a m-3 p m	4 p m-11 p m	Difference
B (7 series)	4,318,000	(6 series) 4,210,000	108,000
D (4 series)	4,242,000	(4 series) 4,137,000	105,000
G (4 series)	4,515,000	(4 series) 4,466,000	49,000
B, D, G (15 series)	4,351,000	(14 series) 4,264,000	87,000 \pm 40,000

As the difference, 87,000, is only a little over two times its probable error, 40,000, there is, again, no proof statistically that the decrease toward evening is real. However, the patterns of the composite curves (charts 1 and 2) show a slight downward trend in the latter part of the day, and with more data and still more accurate technic this may prove to be significant.

Observations—Variations in total counts from 12 m through 7 a m were as follows (table 4 chart 2)

1 series 8 counts active (38)

3 series 8 counts inactive (39-41)

—
4 series total

Results—Although the number of series is limited, the data indicate again the constancy of the red blood cell count during a limited period of time. There are no variations outside the limit of error for the technic and no characteristic pattern. It is probable that the increase and decrease of cells during the twenty-four hour period are so gradual that the differences appear only between counts for days, as will be noted in the discussion of the longer series.

VARIATIONS DURING LONGER PERIODS

Although the fluctuations during eight hour periods are so slight that they cannot be proved significant statistically with the amount of data on hand, the variations from day to day may be real. One day, Aug 3 1929, showing an actual difference (i.e., above the limit of error) from the one preceding (Aug 1, 1929) and the one following (Aug 4, 1929) is seen in the twelve day series in table 5. The test for the significance of the difference between days' counts is the same as that used for the difference between two pipets. Study on this particular phase of the problem is still in progress (Smith,³ 1930). It is probable that these fluctuations and the wider distribution of the

TABLE 5—Total Red Counts on Subject B (Twelve Series in Sixteen Day Period)

Date	Time	Condition	Total Red Mean in Thousands	Probable Error	Difference × Probable Error
7/22/29	8 3	Inactive	4,295	±23	2 1
7/23/29	4 11	Inactive	4,236	±17	
7/26/29	1 11	Inactive	4,205	±13	1 4
7/27/29	8 3	Active	4,281	±17	
7/28/29	8 3	Inactive	4,255	±16	3 6
7/30/29	12 7	Inactive	4,215	±10	
7/31/29	4 11	Inactive	4,223	± 4	1 1
8/ 1/29	8 1	Inactive	4,248	± 7	
8/ 3/29	12 7	Inactive	4,375	± 9	0 5
8/ 4/29	12 7	Inactive	4,283	± 8	
8/ 5/29	1 11	Inactive	4,258	± 7	2 0
8/ 6/29	8 1	Active	4,278	±10	

cells as indicated by the larger standard deviations for most of the longer series are related (table 6). Nevertheless, it is interesting to see how closely the averages for the same person compare for different times of the year. The February, 1929, average for A (3,989,000) is significantly different from the summer average of 1928 (4,131,000), and the one of February-March, 1929 (4,123,000), but the difference between the latter two is not significant according to its probable error. Too much weight cannot be placed on the average, 3,989,000 (February, 1929), because it represents counts for only four days. The twenty-two day count taken later in February and March of the same year is interesting, as the subject was receiving spleen-marrow medication. The

3 Smith, C. Normal Variations in Red-Blood-Cell Counts Over Long Periods of Time, *Anat Rec* 45 278, 1930

means for B for 1928, 1929 and 1930 are so nearly alike that their differences are about equal to their probable errors. The data for both A and B give no evidence of marked seasonal variation.

HEMOGLOBIN DETERMINATIONS

Technic—As with the counting of the erythrocytes, the problem in estimating the hemoglobin content of the blood is the acquisition of an accurate technic. Although Van Slyke's method is acknowledged to be the most accurate, the Dubosq colorimeter with the hemoglobin attachment was chosen as the apparatus with which determinations could be made as quickly and as simply as possible.

TABLE 6—Total Red Blood Cell Counts Over Longer Periods (in Thousands)

Subject	Date	Season	Mean	Probable Error	Standard Deviation	Coefficient of Probable Variation, Error,			Number
						Probable Error	per Cent	per Cent	
A	1928	Summer	4,131	± 12	240	± 9	5.8	± 0.2	173
	1929	February	3,939	± 13	160	± 10	4.0	± 0.2	64
	1929	February March	4,123	± 17	120	± 12	2.9	± 0.3	22
B	1928	Summer	4,308	± 20	285	± 14	6.6	± 0.3	96
	1929	Summer	4,288	± 6	94	± 4	2.2	± 0.1	116
	1930	January February	4,267	± 27	279	± 19	6.5	± 0.4	51
D	1929	Autumn	4,256	± 35	467	± 25	11.0	± 0.6	80
E	1929	Spring	4,241	± 27	295	± 19	7.0	± 0.5	56
G	1930	Spring	4,496	± 38	398	± 27	8.0	± 0.6	71
H	1929	Autumn	4,407	± 28	311	± 19	7.1	± 0.4	58

A n* = 173 determinations in 19 days
 n = 64 determinations in 4 days
 B n = 96 determinations in 7 days
 n = 116 determinations in 15 days

* In all other series n also indicates the number of days counted.

The errors inherent in the method are different from those in total counting. The measuring and the dilution of the blood can be made easily. The wrong angle of the mirror, an inadequate source of light and fatigue of the observer may contribute to the inaccuracy of the results. Osgood⁴ (1926) found errors as large as 12 per cent in hemoglobin estimations with the Bausch and Lomb Newcomer Hemoglobinometer. As many determinations recorded in this paper were made at night, most values were obtained with light through an 8 inch (20.32 cm) Corning daylight disk, although some were made with northern light and some with a daylight bulb. Comparative figures were obtained on the same blood before this procedure was adopted, and the results were found to be practically the same. In series in which determina-

4 Osgood, E. E. Hemoglobin, Color Index, Saturation Index and Volume Index Standards, Arch. Int. Med. **37**: 685 (May) 1926.

tions were made every half hour, the readings were taken at twenty, twenty-five and twenty-eight minutes after dilution, and in those made every hour, thirty, thirty-five and thirty-eight minutes later. The number of grams given for each hour is the mean of at least nine readings. The yellow filter used throughout this work gave a value of about 3.25 Gm. less than that obtained with the Van Slyke apparatus for the same blood.

The same test for the accuracy of the method was used as for the total counts. Twenty readings were made from the same pipet, and a coefficient of variation less than 1 per cent with a probable error less than 0.1 per cent could be obtained. Two pipets filled from the same drop of blood were found to have means the difference of which was less than two times its probable error. Despite this precision and care in the uniform lighting of the mirror, variations have appeared in the series of daily determinations over a long period of time which are hard to understand.

Observations—Variations in hemoglobin determinations from 8 a. m. through 3 p. m. were as follows (table 7, chart 1)

8 series 16-20 determinations active (1-8)

5 series 8-16 determinations inactive (9-13)

Results—The hemoglobin determinations fluctuate very little during the day, and the slight changes that appear lie within the limit of error for the method. As with the curves for the total counts, a slight depression is seen in the afternoon in the "composite curve" (chart 1) plotted from data for both the active and the inactive days. The means and their probable errors were computed for the morning and afternoon figures with the following results:

8 a. m. through 11 a. m.	12 m. through 3 p. m.
n = 49 (series 1-13)	n = 52 (series 1-13)
$\bar{a} = 10.279 \pm 0.041$	$\bar{a} = 10.217 \pm 0.043$
difference = 0.062 ± 0.059	

As the difference is almost equal to its probable error, there is no reason from these data to believe that the decrease in value in hemoglobin is a real diminution.

Observations—Variations in hemoglobin determinations from 4 p. m. through 11 p. m. and 12 m. through 7 a. m. were as follows (table 7, chart 1)

5 series 4-11 inactive (14-18)

7 series 12-7 inactive (19-25)

Results—From both chart 1 and table 7 it is apparent that the hemoglobin values do not change significantly within short periods of time. When the determinations for subjects B and E are compared for the different times of day, it would seem that those for the afternoon and evening were higher than those for the daytime. However, if the differences between the means and their probable errors are computed, it is found that they are not real.

TABLE 7—*Hemoglobin Determinations (Grams per Hundred Cubic Centimeters of Blood)*

Subject	Date	Mean	8 a m Through 3 p m		Active (18)		Inactive (913)		Original Data Table 12	
			Probable Error	Standard Deviation	Probable Error	Coefficient of Variation, per Cent	Probable Error	Error, per Cent	Number	
1	A	8/ 2/28	10 191	±0 012	0 073	±0 008	0 72	±0 081	19	
2		8/ 3/28	10 215	±0 012	0 075	±0 009	0 78	±0 085	18	
3		2/16/29	10 086	±0 02	0 113	±0 014	1 12	±0 137	16	
4		2/17/29	10 100	±0 013	0 075	±0 009	0 74	±0 091	16	
5		2/22/29	10 220	±0 005	0 030	±0 004	0 29	±0 036	16	
6	B	8/10/28	10 180	±0 017	0 096	±0 012	0 94	±0 115	16	
7		8/14/28	10 518	±0 028	0 164	±0 020	1 56	±0 191	16	
8		8/15/28	10 123	±0 008	0 044	±0 005	0 43	±0 053	16	
9		5/27/29	10 186	±0 013	0 052	±0 009	0 51	±0 093	8	
10		8/ 1/29	10 700						8	
11	E	5/ 5/29	10 445	±0 020	0 113	±0 014	1 08	±0 132	16	
12		6/ 4/29	10 141	±0 019	0 072	±0 013	0 71	±0 129	8	
13		6/ 5/29	10 138	±0 010	0 039	±0 007	0 38	±0 069	8	
4 p m Through 11 p m										
14	B	7/31/29	10 699	±0 009	0 033	±0 006	0 31	±0 036	8	
15		8/ 5/29	10 535	±0 009	0 035	±0 006	0 33	±0 060	8	
16	E	6/15/29	10 528	±0 029	0 110	±0 020	1 04	±0 190	8	
17		6/16/29	10 631	±0 028	0 109	±0 020	1 03	±0 188	8	
18		6/17/29	10 534	±0 012	0 047	±0 009	0 45	±0 082	8	
12 m Through 7 a m										
19	B	7/30/29	10 773	±0 027	0 107	±0 019	0 99	±0 180	8	
20		8/ 3/29	10 700						8	
21		8/ 4/29	10 715	±0 007	0 026	±0 005	0 24	±0 044	8	
22	E	6/19/29	10 559	±0 022	0 083	±0 015	0 79	±0 144	8	
23		6/20/29	10 455	±0 007	0 026	±0 005	0 25	±0 045	8	
24		6/21/29	10 333	±0 008	0 029	±0 005	0 23	±0 051	8	
25		6/23/29	10 45	±0 022	0 084	±0 015	0 80	±0 146	8	

The differences between day, evening and night hemoglobin determinations in subjects B and E were as follows

1	2	3
8 a m through 3 p m	4 p m through 11 p m	12 m through 7 a m
10 304 ± 0 053	10 585 ± 0 231	10 569 ± 0 043
Difference between 1 and 2 = 0 281 ± 0 237		
Difference between 2 and 3 = 0 016 ± 0 235		

VARIATIONS DURING LONGER PERIODS

The changes in the hemoglobin values over longer periods of time may be real as are those of the total red counts, but as determined with the Duboscq colorimeter they do not always parallel those of the

cells These are the variations mentioned previously which are difficult to understand if it is assumed, as many do, that the hemoglobin values vary directly with the total red counts Although the total counts for subject A for the summer of 1928 and February-March, 1929, are not significantly different, the hemoglobin determination for the same periods are (table 8) A real difference is also found between the hemoglobin values for 1928-1929 and 1929-1930 for subject B, whose total counts were not found to vary from one year to another

TABLE 8—*Hemoglobin Determinations Over Longer Periods (Grams per Hundred Cubic Centimeters of Blood)*

Subject	Date	Season	Mean	Probable Error	Standard Deviation	Probable Error	Coefficient of Variation, Probable Error, per Cent		Number
							per Cent	per Cent	
A	1928	Summer	10.41	0.023	0.36	0.017	3.4	0.16	108
	1929	February-March	10.21	0.03	0.22	0.02	2.2	0.23	22
B	1928	Summer	10.40	0.037	0.39	0.025	3.9	0.25	56
	1929	Summer	10.62	0.018	0.20	0.013	1.9	0.12	56
	1930	January-February	10.346	0.059	0.615	0.041	5.94	0.401	50
D	1929	Autumn	10.21	0.015	0.581	0.032	5.60	0.313	71
E	1929	Spring	10.41	0.012	0.17	0.009	1.6	0.08	87
H	1929	Autumn	10.201	0.072	0.768	0.077	5.57	0.362	54
A n* = 108 determinations in 11 days									
B n = 56 determinations in 4 days in 1928									
n = 56 determinations in 7 days in 1929									
E n = 87 determinations in 10 days									

* In all other series n also indicates the number of days counted

The differences between the means and their probable errors were as follows

A Difference 1928-1929 = 0.20 ± 0.037

B Difference 1929-1930 = 0.054 ± 0.069

B Difference 1929-1930 = 0.274 ± 0.062

B Difference 1928-1929 = 0.220 ± 0.039

COMMENT

Total Red Counts—As in the study of the leukocytes, much of the previous work on red blood corpuscles has been on the determination of a normal average derived from values for many persons rather than from daily variations in individuals Of those who have worked on the latter phase of the erythrocyte problem, some believe in a constant number and some in a widely varying one Table 9 reviews in a brief way some of the evidence for and against a fluctuating red blood cell count According to these investigators, there may be no

real variations in a day (Lyon,⁵ Nonnenbruch,⁶ and Rud⁷), small variations (Hayem,⁸ Reinert,⁹ Ward,¹⁰ Craandyk,¹¹ Komocki,¹² Leake, Kohl and Stebbins,¹³ and Stebbins and Leake¹⁴) or large variations (Schwinge,¹⁵ Bing,¹⁶ Biering,¹⁷ Lasch and Billich,¹⁸ Doan and Zelfas¹⁹ and Sabin²⁰)

A sharp line cannot be drawn in this previous work between "real variations" in a day and "small variations" for at least two reasons. The first is that the figures represent averages for different numbers of hours, and the second that the error involved in the technic is not known

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TABLE 9—Variations in Red Blood Cells During the Day and from Day to Day

Author	Date	Coefficient of variation, %	Variations in a Day		Variations Between Days		Comment
			Small	Large	Small	Large	
Hansen	1876 1889		Very slight beyond error				More in young
Il von	1881		Slight within error		Real	Not "fairly" large	16 days, 4 observations each day (17% coefficient of variation) (Real, probably not real) 12 days, 3 times a day
Reinecke, W. Halle	1889				Real		7 days, every 2 hours (almost 6% coefficient of variation during 15 to 21 hour periods)
Reinert	1891	2.97	Real		Coefficient of variation, 5%		2 series, 2 and 3 days, 4 series every 2 hours 8 a m to 8 p m, coefficient of variation about 5%
Schwinge	1898						9 days 4 persons average difference between a m and p m 250,000
Ward	1904		Vary through range 5%		No essential difference		7 consecutive days
Burker, K. München med. Wehnschr	1912	1.8					
Bing	1919	2.3		Range 6700,000 in a day			1 men, 7 women, 2 counts early and late morning, 7 increase, 3 decrease
Crandyk	1918 1919	3.1 3.4	Vary 50,000 to 470,000		Agrees with Burker	Large 1,000,000	Largest absolute difference, 2 1/2 million, largest daily variation, 1 1/4 million, variations characteristic of individual
Bierring	1920	3.2	Constant	500,000 outside error			5 series, 26 times daily 1 series, 57 days each, 4 series weekly, 3 1/2 months, 3 series, 67 determinations, 6 months
Nonnenbruch	1921		No real		Rare and small		Difference between successive counts of same individual less than 200,000
Rud	1922 1923	2.0			Small		
Konocki	1924 1927		Small				10 cases of anemia, every 2 hours, 8 a m through 6 p m, average variation 250,000
Mills, E. S. Arch. Int. Med.	1925			Large			3 times in 24 hours, average difference 1,000,000, smallest 130,000, may be 900,000 in 24 hours
Lisch and Billhe	1925 1926	2.6		Large			2 hour counts, 15 minute intervals, difference of 1,000,000
Doan and Zeifus	1927						Coefficient for day 1.6%
Stebbins and Leake	1927		Small				Average diurnal variation for women, 310,000, for men, 345,000
Leake, Kohl and Stebbins	1927						Range of 1,000,000
Leake, Kohl and Stebbins	1928						

in each case. When the latter is not given, it is impossible to evaluate the data except by comparison with data presented in this paper. It has been shown that the average range for the 8 a. m.-3 p. m. counts for 19 series is $251,000 \pm 18,000$, with a maximum of 490,000, and the coefficient of variation for over half the counts is seen to be less than 2 per cent (table 4). Therefore, figures that are given as indicating small variations may well be within the limit of error of fairly accurate technic (Ward,¹⁰ Craandyk,¹¹ Komocki,¹² Leake, Kohl and Stebbins¹³ and Stebbins and Leake¹⁴). There is no way to judge the validity of the conclusions of Hayem,⁸ and those of Reinert⁹ appear to be according to his data.

The large variations that are cited are outside the limit of error if that has been determined for the method and found to be small. Bing,¹⁶ Biering¹⁷ and Lasch and Billich¹⁸ have given values for the error involved in the method (23, 32 and 26 per cent, respectively, table 9). However, Biering¹⁷ eliminated one large variation from his result as due to technic, previously noted by Rud,⁷ and therefore lessened the worth of the coefficient of variation quoted by him. Although the range of cells in twenty-four hours noted by Lasch and Billich¹⁸ is larger, as might be expected, than that given for eight hour periods in this paper, it is also greater than the differences usually found between daily counts over longer periods of time (table 5 and unpublished data). The appraisal of the figures given by Bing¹⁶ and Lasch and Billich¹⁸ is also rendered more difficult because they found differences in the cell content of the blood from different parts of the body, which is not in accordance with other work on this phase of the erythrocyte problem (Reichel and Monasterio,²¹ 1929). Schwinge,¹⁵ Doan and Zervas¹⁹ and Sabin²⁰ gave no information as to the error involved in their technic. Sabin²⁰ stated her conclusions concerning the fluctuations in total red cell count as follows: "Sabin and Doan and Zervas have shown that the delivery of red cells from the marrow is rhythmic with a range of about 1,000,000 cells between the high and low counts each day, as far as their observations have gone the rhythm does not follow that of the white cells, with the marked rise in the afternoon, but rather the high points come both morning and afternoon."

The data presented in this paper support the conclusions that within short periods of time, certainly the eight hour periods investigated, the total red blood cell count is practically constant, and that any fluctuations present are within the limit of error of the method. In order to

21 Reichel, J., and Monasterio, G. *Beitrage zur Frage der numerischen Verteilung der Erythrocyten und Leucocyten an der Peripherie*, Klin. Wchnschr. 8 1712, 1929.

evaluate correctly normal changes in blood cell content or those due to experimental procedure, the accuracy of the technician must be definitely known. The parallelism of the coefficients of variations for cells within pipets with those for day counts by the same technician is striking (tables 3 and 4). Furthermore, increased efficiency on the part of the technician always resulted in a decreased value for the coefficient of variation for the periods counted.

The depression of the curve for red cells in the afternoon has been reported by Reineit,⁹ Ward¹⁰ and Rud.⁷ Reineit⁹ found a real difference between 12 and 2 o'clock, and Ward,¹⁰ following Reineit⁹ in method, found an average decrease of 250,000 cells in the late afternoon counts of 4 men in a nine day series. Ward¹⁰ also made 150 isolated morning and 185 afternoon counts on different persons and obtained an average difference of 300,000 cells. Rud.⁷ described diminutions at the end of the day which do not pass beyond the limits of error for the method, but he added that on the other hand they come with such regularity that one is not able to refrain from thinking that they are not fortuitous. The results obtained in this study confirm Rud's point of view. Although the morning and afternoon and the day and evening counts show a decrease in the last part of the day, it cannot be proved statistically with the amount of data on hand.

The drop after meals reported by Hayem,⁸ Reineit⁹ and Leake, Kohl and Stebbins¹³ is found uncertain by Lyon,⁵ Bing¹⁰ and Rud.⁷ Reineit⁹ quoted Vierordt as believing that the decrease is due to the dilution of the blood after the intake of water. However, Bing¹⁰ found no decrease after starving persons for twelve hours and then having them drink a liter of water, and Rud.⁷ found no clear evidence that the adsorption of water played any rôle in the variations of red cells. From the data collected in this study there is no evidence that the intake of food or water influences the total red blood cell count. Breakfast was always eaten just before the first count in the day series and lunch usually at 1 or 1:30 p. m., in the 4 to 11 p. m. series dinner came at 6:30 p. m., and during the night no food was taken. In the cases in which nothing was eaten after breakfast, there was no increase in the number of cells during the day, although fasting is said to result in larger counts (Hayem,⁸ Dupre after Reineit⁹). Conclusions cannot be drawn, however, concerning the effect of fasting on the red cell count as the amount of data is too small and the time of fasting too short.

The curve for the numbers of red cells in the peripheral blood during the day and night is in no way correlated with that for the leukocytes. The marked fluctuations and the increase in the afternoon which are characteristic of the curves of white cells of fairly active

people (Sabin, Cunningham, Doan and Kindwall,²² 1925, Smith and McDowell,²³ 1929) are not seen in red cell curves made at the same time (unpublished data). This has been noted by Sabin, Cunningham, Doan and Kindwall²² and by Doan and Zeifas.¹⁹ Glaser²⁴ (1928) expressed the belief, on the contrary, that the red and white counts show analogous changes in his study of Vidal's hemoclastic crisis.

Significant changes have been found to be present between counts for days in a long series of successive daily counts (table 5 and Smith³). These variations will not necessarily show if the period is short, e g, the seven day series of Burkert²⁵ and Rud,⁷ who found no essential differences. In the longer series of Rud⁷ the counts are too scattered to give accurate information, but he concluded from them that the real variations present are relatively rare and small. One must therefore believe with Rous²⁶ in "the existence under ordinary circumstances of a delicately balanced coordination between the rates of cell formation and cell destruction," for the variations of red cells during short periods of time are so small as to be within the limit of error of the method and appear as real deviations only in longer series of counts.

Hemoglobin Determinations—Variations in hemoglobin determinations are similar and parallel to those of the total red counts that have been described by Ward,¹⁰ Doan and Sabin²⁷ (1927), Doan and Zerkas¹⁹ and Ponder and Millar.²⁸ Doan and Zeifas¹⁹ and Rud⁷ stated that the changes are smaller than those of the total counts, and Rud added, less frequent. Doan and Sabin,²⁷ however, pointed out in their work on experimental tuberculosis that the increases in hemoglobin may precede those in total cells.

Large diurnal variations (in hemoglobin estimations) have been found more frequently than small ones by previous investigators (table

22 Sabin, F R, Cunningham, R S, Doan, C A, and Kindwall, J A. The Normal Rhythm of the White Blood Cells, *Bull Johns Hopkins Hosp* **37** 14, 1925.

23 Smith, C, and McDowell, A M. Normal Rhythm of White Blood Cells in Women, *Arch Int Med* **43** 68 (Jan) 1929.

24 Glaser, F. Vegetatives Nervensystem und Blutzusammensetzung, *Folia haemat* **35** 353, 1928.

25 Burkert, K. Ueber Prufung und Eichung des Sahlischen Hamometers und uber Verbesserungen der Methoden der Erythrozytenzahlung und Hamoglobinstimmung, *Munchen med Wchnschr* **59** 89, 1912.

26 Rous, P. Destruction of the Red Blood Corpuscles in Health and Disease, *Physiol Rev* **3** 75, 1923.

27 Doan, C A and Sabin, F R. Tuberculosis in the Bone Marrow, *J Exper Med* **46** 315, 1927.

28 Ponder E, and Millar, W G. The Measurement of the Diameters of Erythrocytes, *Quart J Exper Physiol* **19** 145, 1928.

10) Schwinge,¹⁷ Ward¹⁰ and Mills²⁰ gave 5 per cent as the size of the variations in a day, while Dreyer, Bazett and Pierce³⁰ and Rabinovitch³¹ found variations of 10 per cent common. Even with one type of apparatus (i.e., the Van Slyke), the variations range from 5 to 10 per cent according to the investigator.

TABLE 10—Daily Variations in Hemoglobin Determinations

Author	Date	Apparatus	Error in Method	Variations in Day	Variations from Day to Day
Reinert ⁹	1891			Quotes Leich- tenstern, highest at 12, lowest at 4	
Schwinge ¹⁵	1898	Fleischel Miescher		5% variation 8 a.m. to 8 p.m.	
Ward ¹⁰	1904	Fleischel	More open to error	Varies directly with red, about 5%	
Terhola, L. Arch. f Gynak. 103: 115, 1914	1914	Fleischel Miescher Sahlh	16 duplicate counts, 0.37% isolated, 26%, 16, 2.7%, isolated count, 1.9%		
Dreyer, Bazett and Pierce ³⁰	1920	Duboseq	0.3% for read- ings	10% in day com- mon, smallest between 5-7 p.m., greater varia- tions in low hemoglobin values	
Rudolf	1922 1923	Autenrieth Königsberger	10 determina- tions, each the average of 5 readings, 1.7%, 1.8%	No real varia- tions	Less frequent than reds, over longer periods within limits of error
Rabinovitch ³¹	1923 1924	Van Slyke		Average range, 20 people, 6 times a day, 12%, p.m. less than a.m.	
Mills ²⁰	1925	Van Slyke, Dare		16 cases of pern- icious anemia, 4, anemia, every 2 hours, 8 a.m. to 8 p.m. varia- tion 5.1% Van Slyke, 5.5% Dare	
Brandt, T. Folia haemat. 12: 177, 1926	1926	Sahlh	1%		
Osgood ⁴	1926	Bausch and Lomb New comer hemo- globinometer Osgood	12% error Maximum not over 2%		
Doan and Zerfas ¹⁹	1927	Duboseq		Varies about one half that of cells and parallels changes in reds	
Ponder and Millar ²⁸	1928	Palmer's colorimetric method	±1.1%	Follows red curves	

²⁹ Mills, E. S. Hourly Hemoglobin Variations in Anemias, Arch. Int. Med. 35: 760 (June) 1925.

³⁰ Dreyer, G., Bazett, H. C., and Pierce, H. F. Diurnal Variations in the Hemoglobin Content of the Blood, Lancet 2: 588 (Sept. 18) 1920.

³¹ Rabinovitch, I. M. Variations of the Percentage of Hemoglobin in Man During the Day, J. Lab. & Clin. Med. 9: 120, 1923-1924.

TABLE 11—*Original Data Red Blood Cell Counts (in Ten Thousands)*

	1	2	3	4	5	6	7	8	9	10	11	12
8 a m	417	406	399	437	433	418	437	422	425	440	451	460
8 30	400	432	437							458		
9	404	388	400	431	429	417	437	423	424	461	455	459
9 30	389	407	440							462		
10	398	400	406	429	434	413	433	424	424	466	476	457
10 30	415	390	417							467		
11	399	414	426	435	423	420	438	425	423	470	467	470
11 30	408	411	403							465		
12	354	404	408	426	427	412	439	429	424	445	462	446
12 30	394	394	414							468		
1	384	385	400	427	426	412	438	424	422	456	452	443
1 30	381	391	420							454		
2	387	399	425	426	423	401	436	422	420	469	464	447
2 30	385	401	398							454		
3	389	403	394	414	427	412	433	425	422	444	455	446
3 30	390	383	417							475		
8 a m			13	14	15	16	17	18	19	20	21	22
8 30			453	458	435	462	434	431	428	457	403	414
9										417		
9 30			438	458	440	447	449	415	422	418	428	403
10										404		
10 30			435	457	430	453	425	425	427	422	415	420
11										432		
11 30			437	455	434	438	422	433	422	431	410	437
12										415		
12 30			439	457	441	444	431	430	425	433	415	422
1										415		
1 30			435	450	430	462	423	419	421	417	402	421
2										421		
2 30			440	446	436	444	433	429	429	418	414	412
3										413		
3 30			444	453	449	443	419	422	424	422	411	411
	23	24	25	26	27	28	29	30	31	32	33	34
4 p m	435	416	421	426	407	424	415	416	410	424	368	446
5	430	426	425	432	409	424	414	414	403	427	387	436
6	413	423	422	426	411	427	413	420	410	424	368	451
7	419	417	421	424	409	425	412	419	394	425	364	436
8	419	427	423	425	412	424	411	419	397	422	375	450
9	428	425	420	426	409	421	415	418	402	422	366	444
10	422	415	420	424	411	422	414	414	403	421	404	448
11	423	415	423	423	412	422	411	396	403	421	364	447
	35	36	37			38	39	40	41	February, 1929		
4 p m	418	472	463	12 m		413	433	438	430	Subject A		
5	420	472	453	12 30		387				400	437	
				1 a m		396	423	443	434	432	424	
6	419	473	451	1 30		401				437	410	
				2		381	426	440	430	379	410	
7	418	472	449	2 30		394				404	413	
				3		372	422	440	428	377	411	
8	419	469	448	3 30		368				420	410	
				4		387	419	436	428	415	400	
9	423	465	447	4 30		371				416	417	
				5		382	421	433	428	404	410	
10	417	466	452	5 30		389				401	422	
				6		391	426	432	423	427	411	
11	422	469	454	6 30		379				409		
				7		386	426	438	425			
				7 30		379						

TABLE 12—Original Data Hemoglobin Determinations (Grams per Hundred Cubic Centimeters)

			1	2	3	4	5	6	7	8	9
S a m			10 25	10 37	9 85	10 08	10 19				10 31
8 30			10 37	10 37	9 91	10 19	10 25				
9			10 25	10 19	10 14	10 19	10 19	10 44	10 57	10 19	10 14
9 30			10 31	10 19	10 08	10 11	10 19	10 12	10 31	10 08	
10			10 25	10 37	10 25	10 08	10 25	10 19	10 37	10 19	10 19
10 30			10 19	10 19	10 14	10 08	10 25	10 14	10 37	10 08	
11			10 19	10 14	10 19	10 25	10 19	10 31	10 44	10 08	10 19
11 30			10 14	10 19	10 08	10 19	10 25	10 31	10 37	10 08	
12			10 19	10 19	10 02	10 14	10 25	10 08	10 37	10 08	10 19
12 30			10 14	10 25	10 19	10 08	10 19	10 14	10 50	10 02	
1			10 19	10 19	9 96	10 02	10 25	10 08	10 50	10 08	10 14
1 30			10 14	10 25	10 02	10 02	10 19	10 10	10 76	10 14	
2			10 08	10 14	10 11	10 02	10 25	10 16	10 50	10 08	10 14
2 30			10 25	10 25	10 02	10 08	10 19	10 25	10 96	10 25	
3			10 19	10 08	10 14	9 96	10 19	10 14	10 44	10 14	10 19
3 30			10 14	10 11	10 25	10 08	10 25	10 14	10 68	10 14	
4			10 14	10 25				10 14	10 63	10 14	
4 30			10 14	10 19				10 14	10 57	10 19	
5			10 08								
	10	11	12	13		14	15	16	17	18	
S a m	10 70	10 63	10 02	10 08	4 p m	10 63	10 50	10 63	10 63	10 57	
8 30		10 44									
9	10 70	10 57	10 19	10 08	5	10 70	10 57	10 57	10 50	10 50	
9 30		10 44									
10	10 70	10 44	10 19	10 14	6	10 70	10 50	10 50	10 63	10 50	
10 30		10 50									
11	10 70	10 50	10 19	10 14	7	10 76	10 50	10 44	10 50	10 50	
11 30		10 41									
12	10 70	10 50	10 19	10 14	8	10 70	10 57	10 76	10 37	10 50	
12 30		10 31									
1	10 70	10 31	10 19	10 19	9	10 70	10 57	10 44	10 76	10 57	
1 30		10 37									
2	10 70	10 31	10 02	10 14	10	10 70	10 50	10 44	10 63	10 63	
2 30		10 37									
3	10 70	10 31	10 14	10 19	11	10 70	10 57	10 44	10 53	10 50	
3 30		10 69									
				19	20	21	22	23	24	25	
12 m				10 70	10 70	10 70	10 63	10 50	10 31	10 50	
1 a m				10 76	10 70	10 70	10 50	10 44	10 31	10 37	
2				10 70	10 70	10 76	10 63	10 44	10 31	10 37	
3				10 70	10 70	10 70	10 50	10 44	10 37	10 63	
4				11 03	10 70	10 70	10 50	10 44	10 37	10 50	

On the other hand, Rud⁷ stated that the hemoglobin values are constant and there is no real variation during the day. In this study the variations in a day have been found to be within the limit of error of the method and, as with the total reds, the afternoon depression was not proved to be significant according to the data on hand. Neither were the means of the day, evening and night counts found to be really dif-

TABLE 13—*Original Data Total Erythrocyte Counts, 10 to 20 Drops from the Same Pipet Number Counted in Eighty Small Squares*

Technician A	1		2		3		4		5		6	
	437	441	434	424	421	413	398	401	420	440	432	418
	144	427	452	409	425	424	398	413	430	426	424	429
	465	458	432	431	421	415	419	374	443	430	440	413
	435	431	423	431	405	412	415	397	452	445	434	423
	431	429	455	412	411	408	407	414	433	455	434	423
	442	483	408	406	433	409	395	418	434	433	419	426
	422	443	424	445	399	417	393	399	440	427	413	426
	417	412	442	421	413	413	412	411	405	429	439	424
	420	431	420	426	408	404	414	412	436	426	428	422
	417	425	418	430	419	390	384	401	431	453	419	426
Technician C	1		2		3							
	477	472	433	403	448	469						
	476	475	451	439	439	440						
	482	482	419	418	433	434						
	475	454	431	415	450	454						
	456	471	424	425	462	447						
	457	456	420	450	455	433						
	466	456	430	430	447	444						
	455	448	431	437	452	439						
	459	461	426	418	458	439						
	451	449	447	418	444	406						
Technician D	1		2		3		4					
	488	481	465	468	431	427	421	424				
	480	483	475	460	425	425	414	424				
	466	461	476	464	415	426	413	420				
	485	473	460	458	420	422	431	428				
	481	472	475	476	427	417	424	424				
			468	470								
Technician F	1		2		3		4					
	393	392	386	396	394	393	393	393				
	393	399	391	390	393	392	394	393				
	394	392	388	389	394	393	392	393				
	390	391	391	390	393	394	393	392				
	391	393	392	391	394	395	394	394				

ferent from each other. A drop after meals has not been noticed (confirming Rud⁷), although Maix³² (1925) described such a reaction after the intake of water.

There is very little literature concerning the variations in hemoglobin values from day to day. Rud⁷ consistent with his belief in the constancy of the total counts, stated that over longer periods of time the variations in hemoglobin determinations are less frequent and

³² Marx, H. Untersuchungen über den Wasseraushalt. Klin. Wchnschr. 4: 2339 (Dec. 3) 1925.

smaller than those of the red cells. According to Lippincott³³ (1927), the hemoglobin is highest in cold months and lowest after the hot months. In this investigation the hemoglobin values have been found to vary during long periods of time, the wider distribution of the observations being reflected in the larger coefficients of variation. Work is being continued on this phase of the problem in its relation to total counts and cell volumes.

SUMMARY

1 Total erythrocyte counts and hemoglobin determinations vary within the limits of error of the methods for short periods of time.

2 Total erythrocyte counts and hemoglobin determinations do not vary significantly in response to rest, moderate activity or food.

3 There may be real differences between total erythrocyte counts and hemoglobin determinations of separate days or between averages for longer periods.

4 The error inherent in the method should always be a known value in investigations involving data of this kind.

³³ Lippincott L. S. Hemoglobin and Erythrocytes in the South, *J. Lab. & Clin. Med.* **12** 679, 1927.

DIFFERENTIAL DIAGNOSIS OF MEDIASTINAL "TUMORS"

ANALYSIS OF EIGHT VERIFIED CASES *

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In 1888, Hare¹ collected 520 cases of mediastinal disease, over 50 per cent of which were due to tumors, mostly of the malignant type. Riegel,² Bennett,³ Eger,⁴ Harris⁵ and Steven⁶ have written monographs on the subject of intrathoracic and mediastinal tumors. Yet mediastinal tumors continue to awaken keen interest in view of their protean manifestations, their diagnostic difficulties and their generally poor prognosis. A review of the literature indicates that there is not a single pathognomonic symptom or sign on which one can depend in the differential diagnosis of mediastinal masses. As has been repeatedly shown, metastasis elsewhere in the body may initiate and dominate the symptomatology. The eight cases here reported originated in the anterior, middle or posterior mediastinum. We have had several cases of esophageal carcinoma, limited strictly to the posterior mediastinum, which we do not include in this report.

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1 Hare, H A. The Pathology, Clinical History and Diagnosis of Affections of the Mediastinum, Other Than Those of the Heart and Aorta, with Tables Giving the Clinical History of 520 Cases, Fothergillian Essay, 1888, Philadelphia, P. Blakiston's Son & Company, 1889

2 Riegel, F. Zur Pathologie und Diagnose der Mediastinaltumoren, Virchows Arch f path Anat **49** 193, 1870

3 Bennett, J R. Cancerous and Other Intrathoracic Growths, Their Natural History and Diagnosis, London, J & A Churchill, 1872

4 Eger, J. Zur Pathologie der Mediastinaltumoren, Inaug Dissert, Breslau, March 26, 1872

5 Harris, V D. Intra-Thoracic Growths, St Barth Hosp Rep **28** 73, 1892

6 Steven, J L. The Pathology of Mediastinal Tumors with Special Reference to Diagnosis, London, H K Lewis & Company, 1892

REPORT OF CASES

CASE 1—*Malignant Endothelioma of the Mediastinum*

M W, a white woman, aged 61, a widow, entered the Albany Hospital in the service of Dr L Whittington Gorham, Nov 6, 1925 She complained of fulness in her throat, with marked hoarseness and occasional attacks of choking There was no history of tuberculosis or cancer in her family Two years before admission to the hospital she had had pneumonia Since then she had been having a chronic cough, and had therefore spent the preceding summer in a sanatorium for tuberculosis The chronic, high-pitched cough had been bothering her for about one and one-half years It had gradually produced more and more of a choking sensation, as the throat seemed to fill up when she coughed

The patient was well developed but thin There were no visible pulsations in her neck, no tracheal tug, no rigidity and no palpable glands The chest was long



Fig 1 (case 1)—*A*, anteroposterior roentgenogram showing the mediastinal tumor shadow at the level of the manubrium sterni, extending approximately 35 cm toward the right side of the chest and having a base 75 cm in extent *B*, right oblique view Note how the barium-filled esophagus winds around anteriorly over the mediastinal mass

and symmetrical Expansion was equal on both sides The lungs were hyperresonant and the breath sounds normal The heart seemed slightly enlarged on percussion The retrosternal dulness across the upper part of the chest measured 11 cm The abdomen was large and tympanitic There were no palpable masses The radial pulses were equal and of good quality

Examination of the blood revealed hemoglobin, 90 per cent, red blood cells, 4,776,000, white blood cells, 6,800, polymorphonuclear leukocytes, 67 per cent, transitionals, 3 per cent, and lymphocytes, 31 per cent The systolic blood pressure was 120 and the diastolic 70 The blood contained 100 mg of sugar and 32 mg of nonprotein nitrogen per hundred cubic centimeters The Wassermann test was negative Urinalysis on one occasion revealed a trace of albumin, no sugar and a

few pus cells. The temperature, pulse and respirations were practically normal throughout the course of the disease.

Roentgen examination showed the lungs to be emphysematous, with no definite evidence of tuberculosis. The heart appeared to be enlarged. At the level of the manubrium of the sternum, there was an oval opaque area extending from the mediastinum a distance of 3.5 cm into the right side of the chest, its base measured 7.5 cm (fig 1). This suggested a mediastinal tumor or an innominate aneurysm. The mass had not been evident in three previous roentgen examinations, the last of which was made seven months before. No pulsations were



Fig 2 (case 1) —Posterior view of mediastinum showing the tumor mass bisected and the trachea laid open. The close apposition of the tumor with the trachea above the tracheal bifurcation is evident.

observed under the fluoroscope. When the patient swallowed barium, the esophagus was observed to be anterior to the mass. Thus, fluoroscopy showed no definite suggestive evidence of an aneurysm.

The paroxysms of choking and coughing grew more severe and the patient gradually became weaker. She died on her twenty-seventh day in the hospital.

Necropsy was performed nine hours post mortem. The veins of the mediastinum and chest wall were much dilated and of a dark color. Thymic tissue was not seen, and the anterior mediastinum contained a normal amount of fat. In the superior mediastinum behind the trachea, a firm mass about the size of a

small lemon could be palpated. It lay slightly to the right of the midline, and its upper border reached about to the level of the sternoclavicular joint. The thoracic organs were removed en masse. Viewed from behind, the esophagus wound around the left side of the tumor and was flattened as it passed over it. The arch of the aorta was pushed forward by the tumor. The trachea lay anteriorly and was only slightly compressed (fig 2). The tumor was an encapsulated

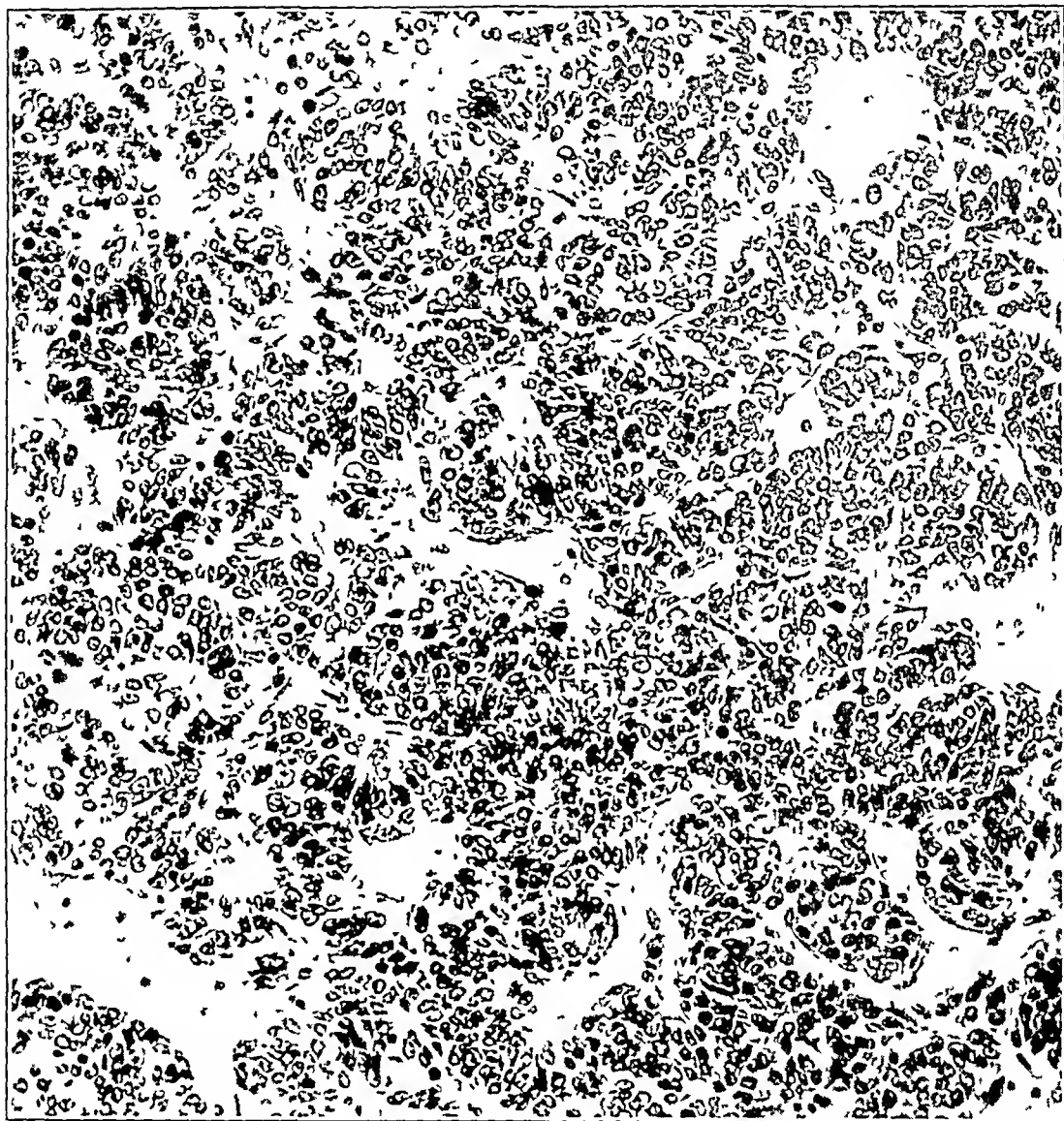


Fig 3 (case 1)—Photomicrograph of the endothelioma. Note the numerous capillary channels around which the tumor cells are arranged in a perithelial manner. Hematoxylin and eosin stains, $\times 208$.

firm mass, not intimately connected with any of the important mediastinal structures. Microscopic examination showed it to be a malignant endothelioma, probably of vascular origin (fig 3). There was no tumor metastasis in the thoracic lymph nodes. The thyroid showed an adenomatous condition with much chronic inflammation.

Comment—Endotheliomas of the mediastinum are infrequently observed. It is interesting to note that this patient dated the onset of her trouble to pneumonia which was followed by a chronic irritating cough. Although her symptoms dated back over one and one-half years, the mediastinal tumor did not become evident until seven months before admission to the hospital, as shown by the repeated roentgen examinations for suspected pulmonary tuberculosis. In the earlier stages of paratracheal or parabronchial tumors, it is not unusual that pulmonary tuberculosis or other chronic respiratory diseases should be suspected, since the only symptom may be an unexplained cough. In a study of thirty-nine cases, Bennett³ found that the most frequent of early local symptoms was some indication of bronchial irritation, such as cough, whether the lungs had or had not been implicated earlier. If expectoration is present it is usually mucoid. The next earliest symptom is dyspnea on exertion. Physical signs are generally lacking entirely until the condition has made considerable progress. Hampeln⁷ expressed the belief that the first sign of mediastinal new growth is a disturbance of the venous-lymphatic flow, causing cyanosis of the face and edema of the neck.

Romano, Ruiz and Waldorp⁸ reported a case of hemangio-endothelioma of the superior anterior mediastinum with metastasis to the left side of the brain, the liver, both suprarenals and both kidneys. The symptoms were predominantly neurologic, and only in the later stages did the intrathoracic tumor become evident by the retraction of the right half of the chest, impaired respirations, diminished resonance, abolished vibrations and edema of the neck. Brustolon and Parere's⁹ case presented a picture of compression of the anterior mediastinum with a sense of imminent death. At autopsy, an endothelioma of the mediastinum was found which had invaded the pleura and right lung. Heuer¹⁰ reported an interesting case of pleural endothelioma which presented itself externally just below the inferior angle of the left scapula. Positive diagnosis before operation was possible by the aspiration of tumor cells.

7 Hampeln, P. Ueber die ersten Anzeichen mediastinaler Neubildungen, *Deutsche med Wchnschr* **47** 1052, 1921.

8 Romano, N., Ruiz, F. N., and Waldorp, C. P. Hemangioendoteloma intra-capilar con localizacion predominante mediastinico pulmonar superior derecho. Con sindrome de epilepsia Jacksoniana del lado derecho y luego hemiplegia dolorosa con afasia motriz y metastasis multiples, *Rev Asoc med argent* **31** 748, 1919.

9 Brustolon, A., and Parere, V. Su di un caso di endoteloma del mediastino, *Arch di pat e clin med* **6** 557, 1927-1928.

10 Heuer, G. J. Intrathoracic Tumors. Experiences with 8 Cases of Tumor of the Thoracic Wall, Pleura and Mediastinum, *Ann Surg* **79** 670, 1924.

CASE 2—Medullary Carcinoma, Primary in the Mediastinum, with Extension to the Lungs and Metastasis to the Brain and Cerebellum

L J, a white man, aged 42, American, married, a creamery manager, entered the Albany Hospital under the care of Dr Arthur H Stem on March 1, 1927. He complained of a sore throat and inability to speak above a whisper. This began with a slightly sore throat about five weeks before admission to the hospital. Shortly afterward, he had difficulty in talking.

His health had usually been good. At times, he had had some headache and dizziness. His eyes had given him no trouble. Recently he had had vomiting. He had become more and more restless, so that he kept his arms and legs in motion

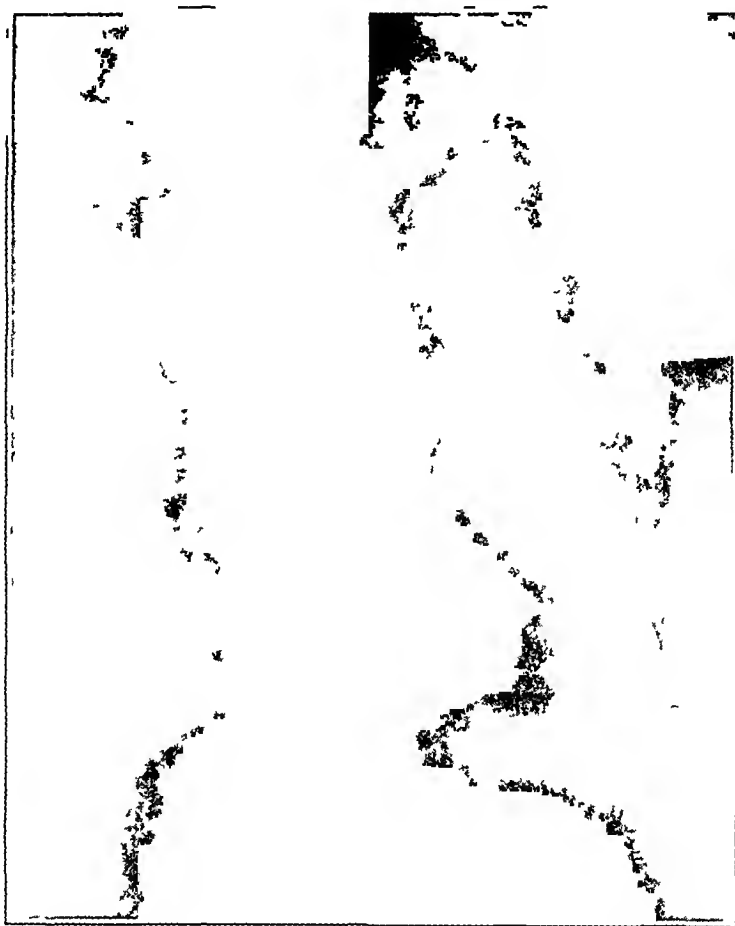


Fig 4 (case 2) —This roentgenogram shows the mediastinal shadow increased in width

much of the time and occasionally had clonic movements of both upper and lower extremities.

It was difficult to make a satisfactory physical examination, because he was drowsy much of the time and unable to focus his attention. He had definite aphasia. All responses were delayed. He was apt to give the same answer to several different questions. He was entirely helpless and had to be fed at all times. There was complete loss of sphincteric control.

Neurologic examination by Dr LaSalle Archambault revealed that the pupils were under the effect of a cycloplegic. The outlines of the disk were ill defined and the veins somewhat full. Ocular excursion was unrestricted. There was a

weakness of the facial musculature on the right side. The tongue deviated to the right. The upper extremities showed bilateral ataxia, more marked on the right. There was no ataxia in the arms, but a definite intention tremor on the right. Reflexes of both upper extremities were equal. The abdominal and cremasteric reflexes were decidedly more active on the left side than on the right. The lower extremities showed paresis, slightly more marked on the right. Knee and ankle jerks seemed more active on the right. There was a partial clonus on the right. No Babinski or Oppenheim sign was present on either side.



Fig 5 (case 2) —Posterior view of the mediastinum showing the tumor in the angle of the tracheal bifurcation

Four days later, the patient was found to be looking persistently to the left. There was a definite spasm of the posterior cervical muscles. The patient continued to speak in a whisper and was definitely disoriented.

A roentgen examination made at this time showed the mediastinum increased in width and the lung markings accentuated (fig 4). Because of the mental condition of the patient, it was difficult to get him to swallow barium to determine whether or not the mass encroached on the posterior mediastinum.

His temperature was subnormal most of the time, the pulse rate ranged between 70 and 140 and the respirations were increased to 65 per minute. His urine was normal. He died eight days after admission to the hospital.

At autopsy, twenty minutes post mortem, an irregularly nodular white tumor mass, approximately 8 by 6 by 4 cm, was found in the superior mediastinum. The greater part of the tumor lay at the bifurcation of the trachea and directly beneath the arch of the aorta (fig 5). The descending portion of the arch was displaced slightly to the left. On sectioning, the tumor showed a hard white

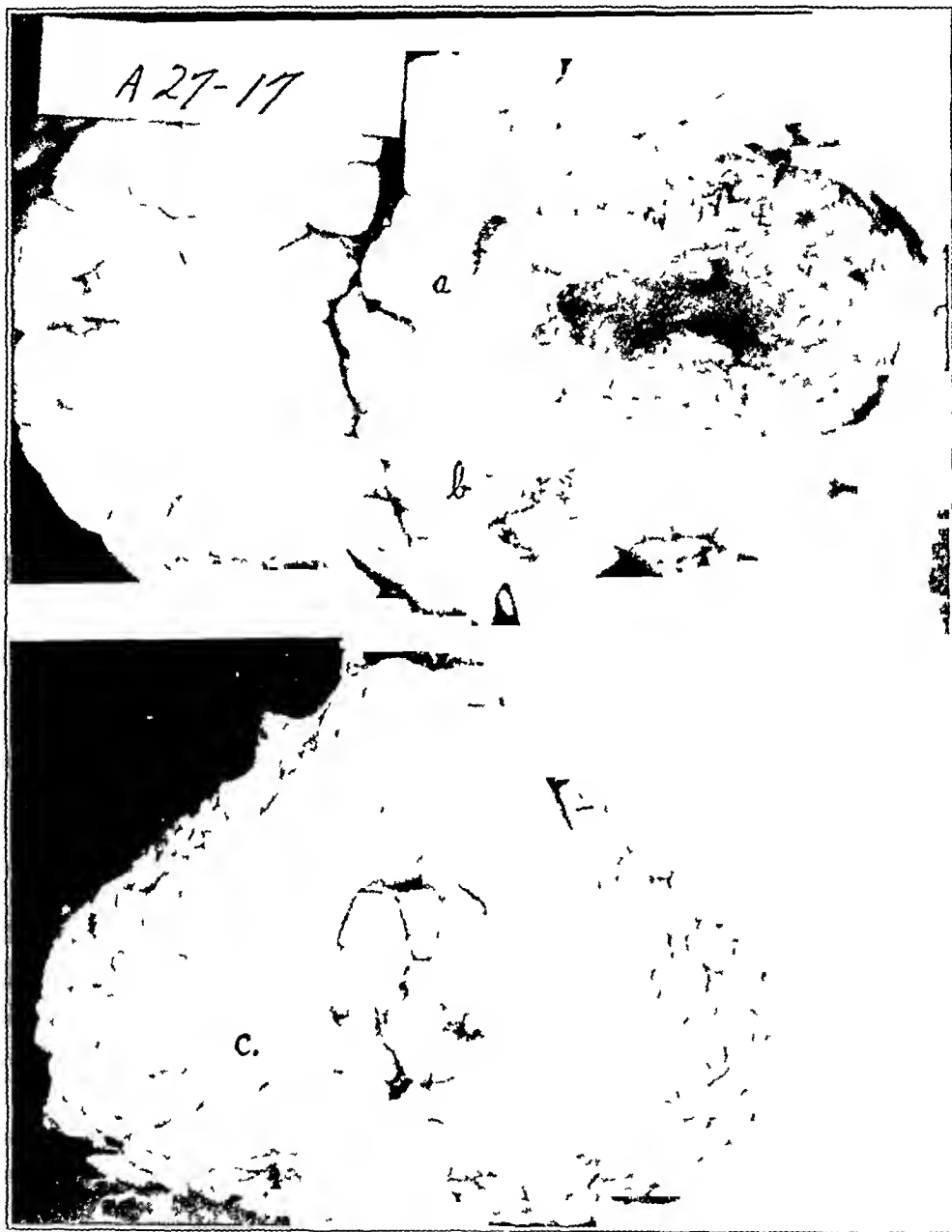


Fig 6 (case 2) —The three metastatic tumor nodules are shown in the cerebrum (*a* and *b*) and cerebellum (*c*)

granular surface with numerous small foci of anthracosis. The trachea, esophagus and aorta were not involved by the tumor mass which, however, invaded the wall of the superior vena cava and projected into the lumen as flat tumor nodules, 0.5 to 2 cm by 2 to 4 cm. The apex of each lung was adherent to the tumor mass by direct extension of the growth. The remainder of both lungs showed bronchopneumonia and edema. The heart was not involved by the tumor.

The brain weighed 1,690 Gm. The meningeal veins stood out prominently, owing to their marked engorgement. The left hemisphere throughout was more voluminous than the right. There was a striking atrophy of both temporal lobes, as shown by the unusual width of the fissures and the corresponding narrowing of the gyri. There was some evidence of intracranial hypertension in the abnormal prominence of the amygdalae. Frontal sectioning showed that the tumor nodule visible over the convexity as a dark round area, about 3 cm wide, extended deeply into the white matter to within 1.5 cm of the mesial surface of the frontal lobe and 2 cm from the basilar surface. Another nodule, 2 by 2.5 cm, distinctly

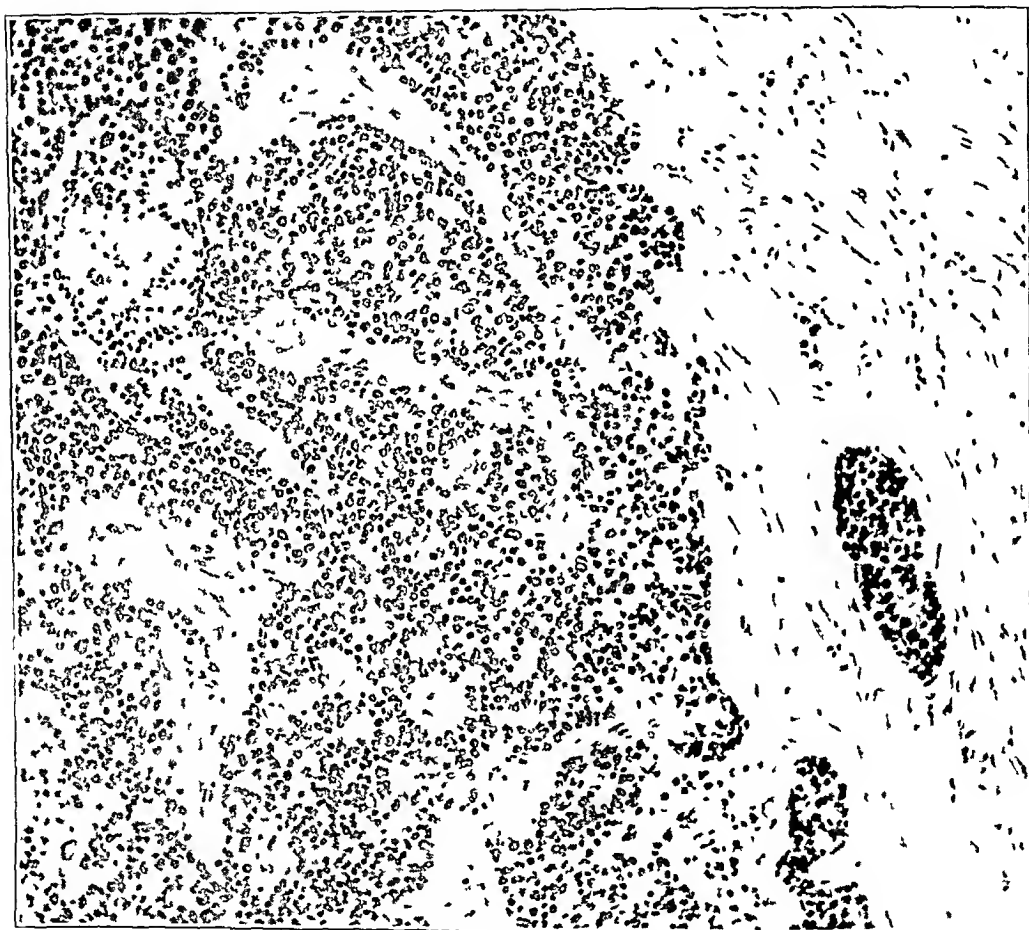


Fig 7 (case 2) —Photomicrograph of the mediastinal tumor showing the highly cellular, medullary character of the growth. Hematoxylin and eosin stains, $\times 137$

oval-shaped and well demarcated, occupied the subcortex of the gyrus rectus. The larger tumor mass extended backward to the level of the anterior horns of the lateral ventricles which were considerably distended. A third tumor nodule, 2 by 2.2 cm, was found immediately beneath the cortex of the left semilunar lobule of the cerebellum (fig 6).

Microscopic sections of the mediastinal tumor, the extensions to the lungs and the metastatic nodules in the brain and cerebellum showed medullary carcinoma (fig 7).

Comment—This patient was admitted to the neurologic service as the symptomatology pointed to a left-sided tumor of the brain. Primary mediastinal tumors not infrequently metastasize to the brain or invade the vertebra and spinal cord. When neurologic symptoms predominate, and especially when symptoms of intrathoracic pressure are masked or do not appear until late, these patients have sometimes been operated on for primary tumor of the brain.

Mix¹¹ reported a case of carcinoma of the posterior mediastinum which pressed on the inferior vena cava below the entrance of the hepatic vein. From a study of the literature, he found that the ratio of primary to secondary mediastinal malignant tumors is 8:1 and the ratio of benign to malignant mediastinal tumors 1:10. Thus, mediastinal tumors are more apt to be primary and malignant. Statistics differ as to which is more common. Carcinomas have been found more frequently by Hale,¹ Mix and Maxwell,¹² and sarcomas more frequently by Harris,⁵ Steven,⁶ Rosenson¹³ and Kott.¹⁴

CASE 3—Thymoma, with Direct Extension to the Pericardium, Heart, Pleura and Diaphragm and Metastasis to the Lungs

D. B., an Italian laborer, aged 19, who had been in this country for a year, was admitted on Oct. 16, 1923, to the Albany Hospital in the service of Dr. Thomas Ordway, complaining of extreme difficulty in breathing. He had been in good health until eighteen days before admission to the hospital, when he stayed at home because of a feeling of weakness, malaise and feverishness. For the next ten days, he was in bed most of the time. Five or six days before admission, after swallowing a piece of steak at dinner, he had a choking spell, turned blue and could not get his breath. This attack lasted for fifteen minutes. On the third and second days before admission, he had similar short attacks of dyspnea and cyanosis. On the day of admission, the distress recurred, and this time persisted.

Examination showed a well developed and well nourished youth sitting up in bed, with his head thrown back in extreme dyspnea and marked cyanosis. He perspired profusely and constantly pointed to his throat. The throat was dry and red with a few small white spots scattered over the posterior pharyngeal wall. The left arm was slightly swollen. The pulse was weaker in this arm than in the right. The heart sounds were of good quality, with no murmurs. Over the left lung there was dulness, with diminished breath sounds posteriorly. Over the base of both lungs coarse moist râles were present.

11 Mix, C. L. Mediastinal Tumors. Full Discussion of Mediastinal Tumors both Benign and Malignant with Classification, Symptomatology, Autopsy, M. Clin. North America **3** 1507, 1920.

12 Maxwell, J. Primary Malignant Intrathoracic Tumors, J. Path. & Bact. **33** 233, 1930.

13 Rosenson, W. Neoplasms of the Mediastinum in Infancy and Childhood. Report of a Case of Ganglioneuroma of the Mediastinum in a Girl of 8 Years, Am. J. Dis. Child. **26** 411 (Nov.) 1923.

14 Kott, B. Ueber Angiosarkome des Mediastinums, Deutsche med. Wchnschr. **48** 1042, 1922.

The white blood cell count was 23,380 The temperature was 99 F, the pulse rate 120 and respirations 28

A roentgen examination was not made, as the patient was moribund The respiratory difficulty and cyanosis increased rapidly The patient died five hours after admission to the hospital

At autopsy, four hours post mortem, a primary mediastinal tumor was found, markedly compressing the trachea and esophagus This tumor (fig 8) probably



Fig 8 (case 3) —Anteroposterior view of the thymic tumor which has been bisected, exposing the pericardial cavity The heart has been removed The trachea is seen as a V-shaped notch at the upper end of the photograph The lobular character of the tumor which fills the entire anterior mediastinum is evident

arose in the thymus because of its position, its lobulated structure and the nature of the type cell which is encountered in the so-called malignant thymoma or thymic lymphocytoma Microscopic examination showed metastases in the lungs as well as a direct extension to the pericardium, heart, adjacent pleura and diaphragm (fig 9)

Comment—Tumors of the thymus continue to hold the interest of clinicians and pathologists alike. They are no longer considered rare. One necessarily thinks of thymic tumors when symptoms of mediastinal pressure in the young are associated with anterior bulging of the chest wall. In this case, the sternum was neither pushed forward



Fig 9 (case 3)—Photomicrograph showing that the thymic tumor cells have densely infiltrated the subepicardial fat and are invading the myocardium. Hematoxylin and eosin stains, $\times 194$.

nor invaded by the anterior mediastinal tumor. In an exhaustive review of the literature, Crosby¹⁵ found that the sternum was actually invaded in 10.1 per cent of the cases of thymic lymphosarcoma.

¹⁵ Crosby, E. H. Personal communication to the authors. This same case is being reported in detail by him.

Danisch and Nedelmann¹⁶ reported a case in a child in whom a malignant thymoma metastasized to the central nervous system and produced symptoms of meningeal irritation with a pleocytosis of tumor cells in the cerebrospinal fluid. In one of Delessert's cases,¹⁷ a lymphosarcoma of the anterior mediastinum penetrated the lumen of the right internal jugular vein and superior vena cava, forming smooth, pink, slightly projecting patches on the internal aspect of these vessels. Delessert expressed the belief that one should be extremely reserved in affirming the thymic origin of malignant tumors of the anterior mediastinum when the characteristic glandular elements of the thymus are absent in the tumor. However, one must remember that although the presence of structures resembling Hassall's corpuscles (well preserved or degenerated and calcific) is of great aid in determining the origin of anterior mediastinal tumors from the thymus, their absence does not mean that they may not have been there in the early stages of the growth of the tumor process. Furthermore, Hassall's corpuscles may be found if a lymphosarcoma of the mediastinal lymph nodes extensively infiltrates the anterior mediastinum.

As emphasized by Jacobson¹⁸ the clinical diagnosis of thymomas is difficult. The correct diagnosis rests on biopsy or autopsy. In the thymoma described by Meeker,¹⁹ repeated biopsies finally revealed the nature of the tumor, which was later confirmed at autopsy.

CASE 4—Hodgkin's Disease of Cervical and Mediastinal Lymph Nodes with Invasion of the Trachea and Metastasis to the Colon and a Meckel's Diverticulum

A T, a white man aged 41, American, married, a detective, entered the Albany Hospital on Sept. 12, 1921, in the service of Dr. Arthur W. Elting, for the removal of a tumor on the left side of the neck. This had been noticed first about a month before admission to the hospital, and during the preceding week it had increased rapidly in size to that of a large hen's egg. The mass was not painful. He had always been in good health except for typhoid fever and pneumonia. His only operation was a tonsillectomy performed during childhood. He had maintained his average weight for some time.

The teeth were in poor condition. On the left side of the neck were irregularly outlined masses, extending from about 1 inch (2.5 cm.) below the left ear along the sternocleidomastoid muscle to about 1 inch above the clavicle. They were fairly

16 Danisch, F., and Nedelmann, E. Bosartiges Thymom bei einem 3½ jährigen Kind mit eigenartiger Metastasierung ins Zentralnervensystem, *Virchows Arch f. path. Anat.* **268**: 492, 1928.

17 Delessert, E. A Clinical Study of Malignant Tumors of the Anterior Mediastinal and Thymic Origin, *Internat. Clin.* **2**: 127, 1922.

18 Jacobson, V. C. Primary Carcinoma of the Thymus, *Arch. Int. Med.* **31**: 847 (June) 1923.

19 Meeker, L. H. Malignant Thymoma. Report of a Case, *Arch. Path.* **5**: 928, 1928. This same case was reported later by Herriman and Rahite (Malignant Thymoma with Metastases, *Am. J. Path.* **5**: 29, 1929).

movable over the underlying structures, but seemed adherent to the skin. Accentuated breath sounds and a few small crepitant rales were heard over the apex of the left lung.

A precipitative specimen of urine had a specific gravity of 1.028, and contained albumin but no sugar. The heavy sediment consisted of pus cells, mucus and squamous epithelial cells.

The tumor mass in the neck was removed and the patient was discharged five days later. On microscopic study, this tumor appeared to be an atypical lymphoma.

Almost nine months later, the patient was readmitted in a moribund condition. During his three days in the hospital, his temperature ranged between 99 and 103 F, the pulse rate averaged 120 and the respirations 45 per minute. The clinical diagnosis was sarcoma of the neck with metastasis to the mediastinum.

Necropsy was performed five hours post mortem. The body was that of a well developed and somewhat obese adult. The left arm was greatly swollen, owing to a marked cellulitis, superficial necrosis and marked edema. Over the tumor mass in the left side of the neck there was a discharging ulcerated area with brawny induration and brownish discoloration of the skin. This discoloration had extended down over the left side of the chest. The enlarged, opaquely white, firm cervical and mediastinal lymph nodes were matted together, the tumor process infiltrated out into the surrounding tissues. Supraclavicular, inguinal and mesenteric lymph nodes were also markedly enlarged. The spleen was not involved. Both lungs showed an acute bronchopneumonia with agonal thrombosis and infarction. Detailed microscopic study showed that this was a case of Hodgkin's disease of the cervical and mediastinal lymph nodes, with invasion of the trachea and adjacent tissues and with metastasis to a Meckel's diverticulum, the colon and mesenteric and inguinal lymph nodes.

Comment—It is generally accepted that although Hodgkin's granuloma may be suspected clinically, the diagnosis rests on the biopsy. Simonds,²⁰ in his general review, found that the most extensively invasive cases of Hodgkin's disease have occurred in the mediastinum and have been thought by many to have originated from the thymus. In this country, Ewing²¹ particularly expressed the belief that the invasive form of mediastinal Hodgkin's disease is in reality a thymic tumor. Lyon²² reported an unusual case of mediastinal Hodgkin's granuloma, with perforation of the anterior chest wall in addition to widespread metastasis. Ewing pronounced Lyon's case another example of thymoma belonging to the Hodgkin's class.

CASE 5—Neurofibroma of the Mediastinal and Inferior Cervical Regions Undergoing Sarcomatous Changes in a Case of von Recklinghausen's Disease

20 Simonds, J. P. Hodgkin's Disease. General Review, *Arch. Path.* **1**: 394 (March) 1926.

21 Ewing, J. The Thymus and Its Tumors. Report of 3 Cases of Thymoma, *Surg. Gynec. Obst.* **22**: 461, 1916, *Neoplastic Diseases*, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 923.

22 Lyon, M. W. Case of Mediastinal Hodgkin's Granuloma with Perforation of the Chest Wall, *Am. J. M. Sc.* **158**: 557, 1919.

W F, a white man, aged 28, American, was admitted on Dec 8, 1927, to the service of Dr George E Beilby, Albany Hospital, with the chief complaint of soreness and "lumps" on both sides of his neck. Outside of the usual diseases of childhood, his general health had been excellent. His tonsils and adenoids had been removed when he was 21 years of age. For the preceding ten years, he had noticed a "goiter," which had remained symptomless until about five months before admission to the hospital. At that time, he noticed a "drawing" and an ache in the right side of his neck. The swelling in the neck had not increased in size, the patient thought it had grown slightly smaller. He had headaches at



Fig 10 (case 5) —The superior mediastinal shadow is much widened, with projection of the tumor mass into the right pleural cavity. The trachea is displaced toward the left.

night while at work in the railroad yards. There had been no tremor of his hands, no sweating or flushing and no loss in weight.

Physical examination revealed a well developed and well nourished young man. There was no motor restlessness. The skin was soft and cool, and showed no flushing. It showed, however, numerous soft tumors, varying in size from about 2 mm to 5 cm in diameter. Some of these cutaneous nodules were sessile, others were pedunculated. They were irregularly distributed all over the body. The skin also showed an irregular brownish pigmentation. A few of these pigmented areas measured from 2 to 5 cm in their largest diameter, but most of them looked like freckles.

The skull was symmetrical. A slight tenderness was present over the right mastoid process. There was some fulness on the right side of the pharynx as though some swelling from the outside were pressing inward. The neck was large and asymmetrical, owing to the presence of large bilateral masses. The right mass was larger, and extended almost to the tip of the mastoid process, beyond the



Fig. 11 (case 5) —Patient with von Recklinghausen's disease. Note the large, almost pendulous, tumor mass in the right side of the neck. This is the externally visible portion of the mediastinal growth shown in figure 10.

midline and down behind the clavicle. Its lower pole was not palpable; pressure on the lower edge caused coughing. The left mass was not so large and was connected across the midline with that on the opposite side. Its lower pole was also not felt. The trachea was markedly displaced to the left. The tumor masses were firm and somewhat irregularly lobulated. A loud systolic bruit could be

heard over the large cervical mass. In addition, many small indurated, discrete nodules were present superficially on both sides of the neck. There were large dilated veins over the right side of the neck and shoulder.

The chest was well developed. The right supraclavicular fossa was almost obliterated by the large tumor mass. The left clavicle appeared more prominent. There was a slight increased convexity of the right side of the chest posteriorly. Chest expansion was good and appeared equal. The lungs were resonant everywhere except for a slight impairment at the right apex. Breath sounds were loud and bronchovesicular, especially at the right apex anteriorly and posteriorly. With the exception of many bilaterally enlarged, indurated nodules in the cervical, axillary, epitrochlear and inguinal regions, examination of the rest of the body yielded no remarkable results.

Roentgen examination revealed a large mass in the mediastinum, extending from the base of the heart into the neck and measuring 14 cm in its greatest transverse diameter. The trachea was displaced toward the left and apparently compressed (fig 10).

The preoperative urinalysis gave no unusual results. The Wassermann test of the blood was negative.

At operation, an exploratory thyroid incision was made. The tumor mass, which extended behind the manubrium sterni, was soft. As total removal was impractical, only a biopsy was performed. The pathologic report was edematous fibroma. The patient was discharged with instructions to return for frequent observation.

He was seen again about two months later. Except for the operative scar, the physical observations were essentially the same as before (fig 11).

About seven months later, the right side of the neck became enormously swollen and fluctuant. On incision of the fluctuant area, degenerating and necrotic material was obtained. A roentgen examination at that time showed a large mass projecting from the neck into the right side of the chest, which displaced the trachea toward the left side. This area measured approximately 15 by 12 cm.

His third and last admission was about ten months after the first. The chief complaint at this time was pain and aching in the left side of his head and in the left shoulder. In the neck were large, asymmetrical, bilateral masses which were more prominent on the right side. The lower pole disappeared behind the sternum. Pressure over this region caused coughing. The left clavicle was still slightly more prominent. Both supraclavicular fossae were now obliterated.

At the second operation, the tumor masses had greatly increased in vascularity. The portion projecting above the sternum was myxomatous and friable. Anteriorly it crossed the midline to the left, evidently invading adjacent muscles. Bleeding was controlled by sutures. Two drains were inserted in the cavity formed by the removal of part of the tumor mass. The pathologic report this time was spindle cell sarcoma rapidly growing and infiltrating adjacent structures.

After leaving the hospital, the patient continued to decline, and died a month later. Autopsy was not permitted. The patient probably died of internal metastasis, judging from the microscopic evidence of invasion of blood vessels by the sarcomatous cells.

Comment—This case has been studied elsewhere in much more detail by one of us (K. H.)²³ Sixty-four similar cases were collected

²³ Hosoi, K. Multiple Neurofibromatosis (von Recklinghausen's Disease), with Special Reference to Malignant Transformation, *Arch Surg* **22** 258 (Feb) 1931.

from the literature and the following conclusions were drawn. Malignant transformation takes place in about 13 per cent of all cases of von Recklinghausen's disease. When this happens, the tumor grows rapidly and tends to recur locally even after repeated operative measures. Metastasis is usually late and frequently absent but may occur early. In some cases, the mere extirpation of a malignant tumor or even a benign one appears to stimulate another neurofibroma distantly located to undergo sarcomatous transformation. Prognosis is poor, the patient succumbing to cachexia and postoperative complications if not to the metastasis.

Banse,²⁴ in 1908, reported an interesting case of fibrosarcoma of the posterior mediastinum with invasion of the vertebrae and the spinal canal, producing the chief symptoms of progressive weakness in both lower extremities. Grawitz' fifth case²⁵ is somewhat similar in that a fibrosarcoma lying between the right apex of the lung and the esophagus infiltrated the vertebral column and compressed the spinal cord. As in our second case, the neurologic symptoms may tend to dominate the picture, drawing one's attention away from the mediastinum. Recently, Crile and Ball²⁶ reported three cases of primary neurogenic tumors of the neck and the mediastinum and collected sixteen similar cases from the literature. They expressed the belief that surgical removal is the only treatment for this type, as radium and roentgen rays do not stop its further growth. We should like to stress the point that an operative attack on mesoblastic tumors of nerve trunks, especially in cases of von Recklinghausen's disease, must be undertaken with great caution.

CASE 6—*Epidermoid Carcinoma of the Right Eparterial Bronchus with Invasion of the Vertebra, Spinal Cord and Nerve Roots*

L. M., a man, aged 53, Hebrew, a clothes presser, was admitted on Oct 20, 1928, to the service of Dr. Thomas Ordway. He had been in fair health until six months previously, when he acquired a cold with bronchitis and a cough which was worse at night. Two months later, he was obliged to stop working as he suffered spells of weakness and dizziness. He was told he had a "spot in his lung," revealed by a roentgen examination made elsewhere. He rested in the mountains for several months, but returned because of a pain in his right shoulder which he understood was "pleurisy." The cough continued to annoy him whenever he lay down, and the throbbing pain in the muscles and soft parts around the right shoulder and axilla became so severe and constant as to interfere with his sleep. At no time did he have night sweats, hemoptysis or much expectoration.

²⁴ Banse, J. Ueber intrathoracische Fibrome, Neurome und Fibrosarkome, Inaug. Dissert., Greifswald, Feb 1, 1908.

²⁵ Grawitz, P. Demonstration einer neuen Gruppe intrathoracakaler Tumoren (Neuro-Fibrosarkome), Deutsche med. Wchnschr. **34** 1123, 1908.

²⁶ Crile, G. W., and Ball, R. P. Primary Nerve Tumors of the Neck and Mediastinum, Surg. Gynec. Obst. **48** 449, 1929.

Anorexia became marked. Frequency of urination occurred both day and night. His past history was uneventful.

The patient was poorly developed and undernourished. The upper third of the right side of the chest was retracted and expansion was diminished over this area. There seemed to be atrophy of the right pectoralis major, with definite tenderness over the soft parts of the right shoulder. Definite dulness was present over the upper third of the right side of the chest anteriorly, with markedly increased vocal and tactile fremitus. Breath sounds were increased over the upper third of both lungs, being particularly noticeable from the third to the sixth dorsal vertebra. The rest of the physical examination was not significant except that the prostate was moderately enlarged, the right lobe was firmer than the left, although not tender.

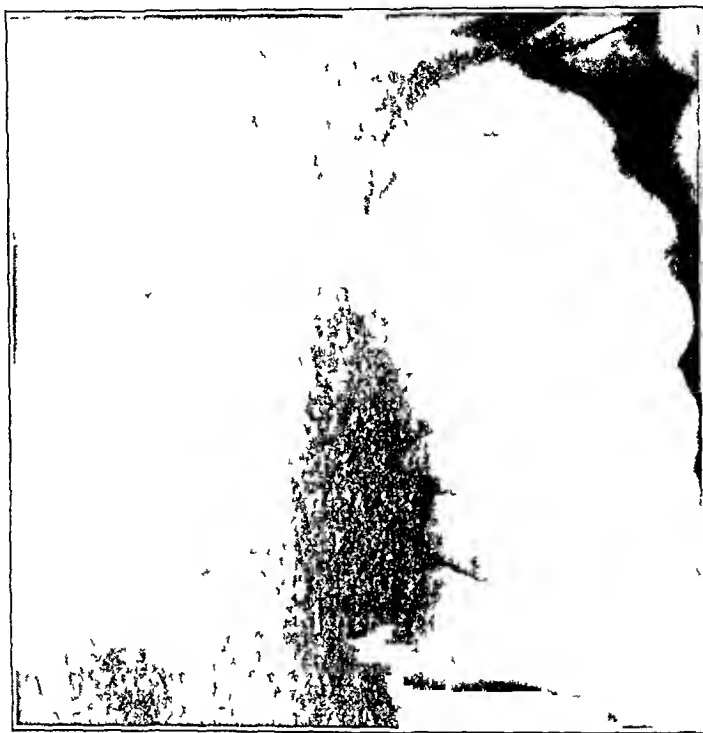


Fig 12 (case 6) —The roentgenogram shows that approximately 8 cm of the fourth rib has been destroyed just distal to the head with erosion of the right lateral border of the third and fourth dorsal vertebrae. The diminished transmission of the rays in the right upper lobe is due to tumor infiltration of the lung parenchyma.

The patient's temperature ranged between normal and 101 F. Numerous examinations of the sputum revealed no tubercle bacilli. The blood chemistry and urinary observations were normal. Tests of kidney function gave normal results. The leukocyte count was 9,200. The Wassermann test was negative.

Roentgen examination showed that the right lateral borders of the third and fourth dorsal vertebrae were not clearly defined and that the trachea deviated toward the right (fig 12). It was felt that these observations in the vertebrae suggested pressure from without.

Neurologic examination by Dr LaSalle Archambault revealed that the facial musculature was relaxed on the right side when at rest. The pupils were slightly

irregular, but reacted actively. The vagus, glossopharyngeal and spinal accessory nerves were apparently normal. There was considerable atrophy of the spinati, rhomboids, pectorals and biceps on the right side. Active movement was about normal in range, with good resistance to passive motion. The scapulohumeral, pectoral, tricipital and radial reflexes were all active. There were no objective sensory losses in the upper extremities. The right pulse was more voluminous than the left. The lower extremities were normal. These observations, together with the roentgen report, were suggestive of a posterior mediastinal lesion com-

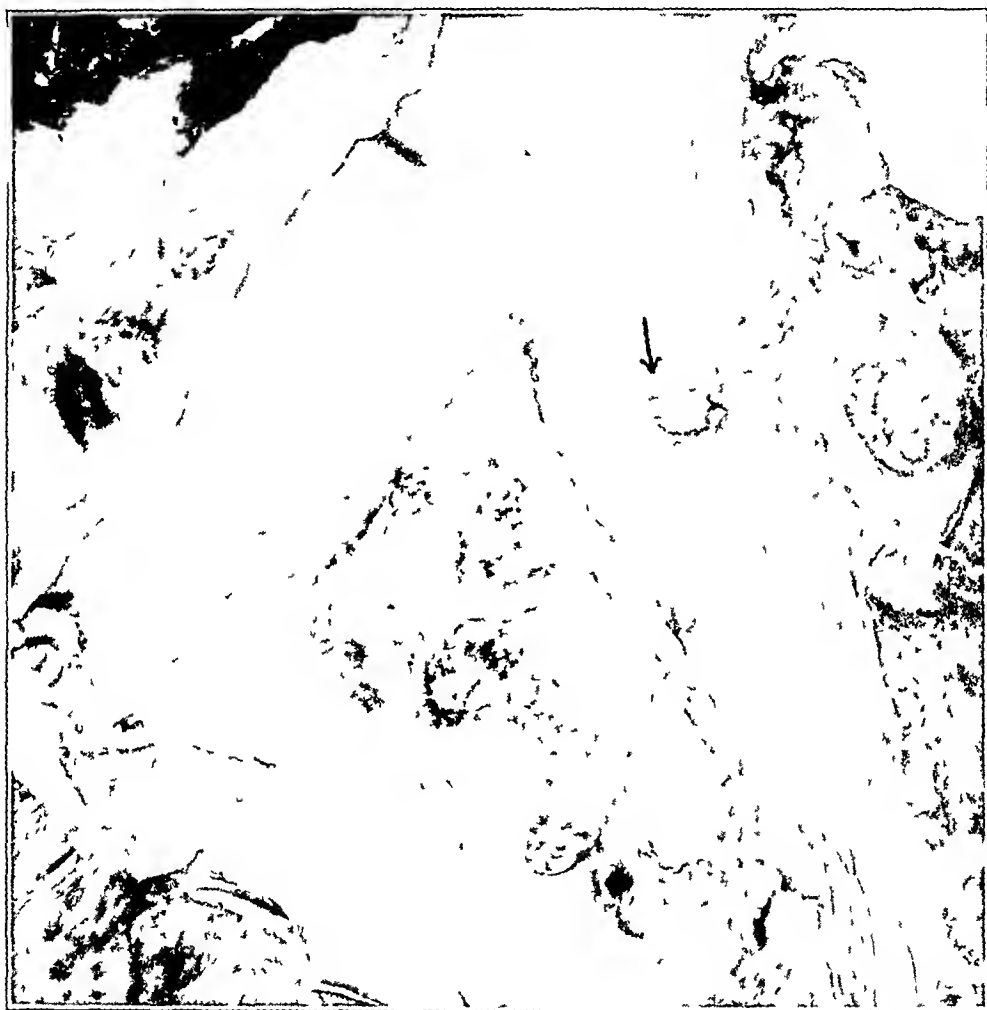


Fig 13 (case 6) —The trachea and bronchi have been opened posteriorly to show the compression of the right eparterial bronchus by the tumor which projects slightly into the lumen of this bronchus (arrow). Note the large tumor masses in the angle of the bifurcation of the trachea.

pressing the spinal cord and to some extent encroaching on the efferent spinal nerve roots of the superior thoracic region of the cord.

About five weeks after the patient entered the hospital a laminectomy was performed for relief from the intolerable pain. The posterior nerve roots were sectioned from the sixth cervical to the sixth thoracic. A specimen removed from the spinal canal at this time revealed a squamous cell carcinoma, invading the bone and soft tissues.

The patient responded well to the operation and had some relief from pain. His cough, however, continued to be a disturbing factor. He was up and about

the ward until about seven weeks after the operation, when paraplegia of the lower extremities with loss of sensation suddenly developed

Neurologic examination at this time showed that there had developed, rather acutely, a transverse syndrome with flaccid paraplegia, sphincteric disturbance, greatly weakened tendon jerks and loss of position, pain and thermal sensibility in the lower extremities. This complication was felt to be due to myelomalacia resulting from thrombosis of the anterior spinal artery or, more probably, to compression or infiltration by the neoplasm.

The patient had more and more difficulty in breathing and died of pulmonary edema on the fifty-third day following the operation.

Necropsy was performed one hour after death. A mediastinal tumor mass was found extending over the dome of the right thoracic cavity and down its posterior wall to about the level of the sixth rib, almost as far as the posterior axillary line (fig 13). The tumor could be seen to cover and invade the vertebral bodies at the level of the third and fourth thoracic vertebrae. The thoracic aorta, trachea and esophagus were not involved. Microscopic examination showed an epidermoid carcinoma of the right eparterial bronchus with invasion of the thoracic vertebrae, of the cord itself and of the nerve trunks with marked compression myelitis. Mediastinal and bronchial lymph nodes were infiltrated with metastatic tumor growth.

Comment—Weller,²⁷ in his general review of the pathology of the subject, stated that primary carcinoma of the lung is rarely diagnosed at a sufficiently early stage to allow for successful surgical intervention, but that the diagnosis is being made more frequently on the living patient than at autopsy. Shennan,²⁸ like Weller, stressed the preponderance of metastasis to the central nervous system. According to Lubarsch,²⁹ tumor of the brain apoplexy and progressive paralysis have been diagnosed frequently in these cases of pulmonary carcinoma with central metastasis. Indeed, Fried³⁰ and Weller stated that the frequency of metastases to the central nervous system as found at autopsy is paralleled by the frequency of clinical cases in which such metastases dominate the picture and lead to erroneous diagnoses. This frequent occurrence of cerebral metastasis has been attributed to the absence of a barrier between the lungs and the brain.

In our case, the confirmatory diagnosis was made by the finding of squamous cell carcinoma in the specimen removed from the spinal canal at the time of laminectomy. In the light of clinical and roentgen

27 Weller, C. V. The Pathology of Primary Carcinoma of the Lung. General Review, *Arch Path* **7** 478 (March) 1929.

28 Shennan, R. Tumors of Mediastinum and Lung, *J Path & Bact* **31** 365, 1928.

29 Lubarsch, O. Einiges zur Sterblichkeits- und Leichenöffnungsstatistik. *Med Klin* **20** 299, 1924.

30 Fried, B. M. Primary Carcinoma of the Lungs. Further Study with Particular Attention to Incidence, Diagnosis, and Metastases to the Central Nervous System, *Arch Int Med* **40** 340 (Sept.) 1927.

observations, the pathologic examination usually confirms the diagnosis by examination of the sputum or pleural fluid for "tumor cells," by examination of the specimen obtained by probatory puncture or through the bronchoscope, and by examination of the superficial lymph nodes containing the metastasis.

If in a case of suspected mediastinal tumor the expectorated or aspirated material contains a large amount of pavement epithelium and fine hairs, the diagnosis of dermoid cyst or teratoma of the mediastinum is suggested. This subject has been exhaustively treated in the excellent papers of Dangschat,³¹ Morris,³² Christian,³³ Hertzler,³⁴ Harris,³⁵ Murphy,³⁶ and Smith and Stone.³⁷ It is to be borne in mind that these tumors of congenital origin can undergo carcinomatous or sarcomatous transformation. They can be successfully enucleated if malignant changes have not yet taken place.

CASE 7—Retrosternal Adenomatous Goiter and Accessory Thyroid in a Case of Enlarged Persistent Thymus

W. E., a white man aged 36, American, single, a clerk, was admitted on May 14, 1929, to the service of Dr. George E. Beilby for a thyroidectomy. Two months before admission to the hospital he first noticed that his heart action was more rapid than previously. At that time there appeared also an increasing dyspnea and excessive perspiration. He had had pneumonia twice within the previous three years, in addition to tonsillitis, influenza and bronchial asthma.

It is interesting to note that his mother had a thyroidectomy the preceding year for exophthalmic goiter and that his sister had a subtotal thyroidectomy also for exophthalmic goiter a month previous to his admission.

After a course of compound solution of iodine, a bilateral subtotal thyroidectomy was performed on the tenth day of his stay in the hospital. At this time, the edematous right lobe of the thyroid was exposed with difficulty as about three fourths of it lay underneath the clavicle. It measured 4 inches (10 cm.) in the largest diameter. The left lobe was similar to the right. Microscopic examination showed it to be an adenoma of the thyroid with degenerative changes.

A few hours after the operation, the patient's temperature, pulse rate and respiratory rate began to rise. In two days, he died of acute bronchopneumonia.

31 Dangschat, B. Beiträge zur Genese, Pathologie und Diagnose der Dermoidcysten und Teratome im Mediastinum anticum, Beitr. z. klin. Chir. **38** 692, 1903.

32 Morris, R. S. Dermoid Cysts of the Mediastinum, M. News **87** 404, 438, 494 and 538, 1905.

33 Christian, H. A. Solid Teratomata of the Mediastinum, J. M. Research **16** 275, 1907.

34 Hertzler. Dermoids of the Mediastinum, Am. J. M. Sc. **152** 165, 1916.

35 Harris, I. B. Mediastinal Dermoid with Report of Case, Ohio State M. J. **15** 547, 1919.

36 Murphy, J. T. Dermoid Cysts in the Thorax, with a Review of the Literature, J. Radiol. **3** 8, 1922.

37 Smith, L. W., and Stone, J. S. Tumors of the Mediastinum in Children, Ann. Surg. **79** 687, 1924.

Necropsy was performed one and one-half hours post mortem. There was acute bronchopneumonia in both lungs. The right lung showed five lobes, instead of the usual three. The superior mediastinum was enlarged, measuring 7 cm across and 10 cm in depth. There was an unusual amount of fat, with marked edema of all the tissues. The thymus (fig 14) was much enlarged. Stumps of thyroid tissue on each lateral aspect of the trachea were still present. No signs of infection or of hemorrhage were evident. The right kidney, normal in size and appearance, lay on the lateral side of the promontory of the sacrum. On micro-



Fig 14 (case 7) —Anterior view of the thoracic structures. Note the enlarged persistent thymus which has pushed the upper lobes of the lungs apart. The remains of the thyroid are seen above the thymus (arrow).

scopic examination, the thymus consisted of many lymphoid elements, with the persistence of numerous well formed Hassall's corpuscles. Serial sections of several pieces of the enlarged thymus revealed a pea-sized island of accessory thyroid tissue (fig 15), many of the acini of which were empty while a number of them contained colloid material. Another anomaly observed was the presence of gland tubules, lined by cuboidal epithelium, in juxtaposition with Hassall's corpuscles.

Comment—It is seen that this patient presented a number of congenital abnormalities, accessory lobes in the right lung, an enlarged persistent thymus, an accessory thyroid embedded in the thymus, retrosternal thyroid and malposition of the right kidney. In addition, there was a familial predisposition to goiter. Experience has shown that congenital defects are often multiple.

Accessory thyroid tissue is most commonly found along the course of the thyroglossal duct, particularly in the region of the hyoid bone.

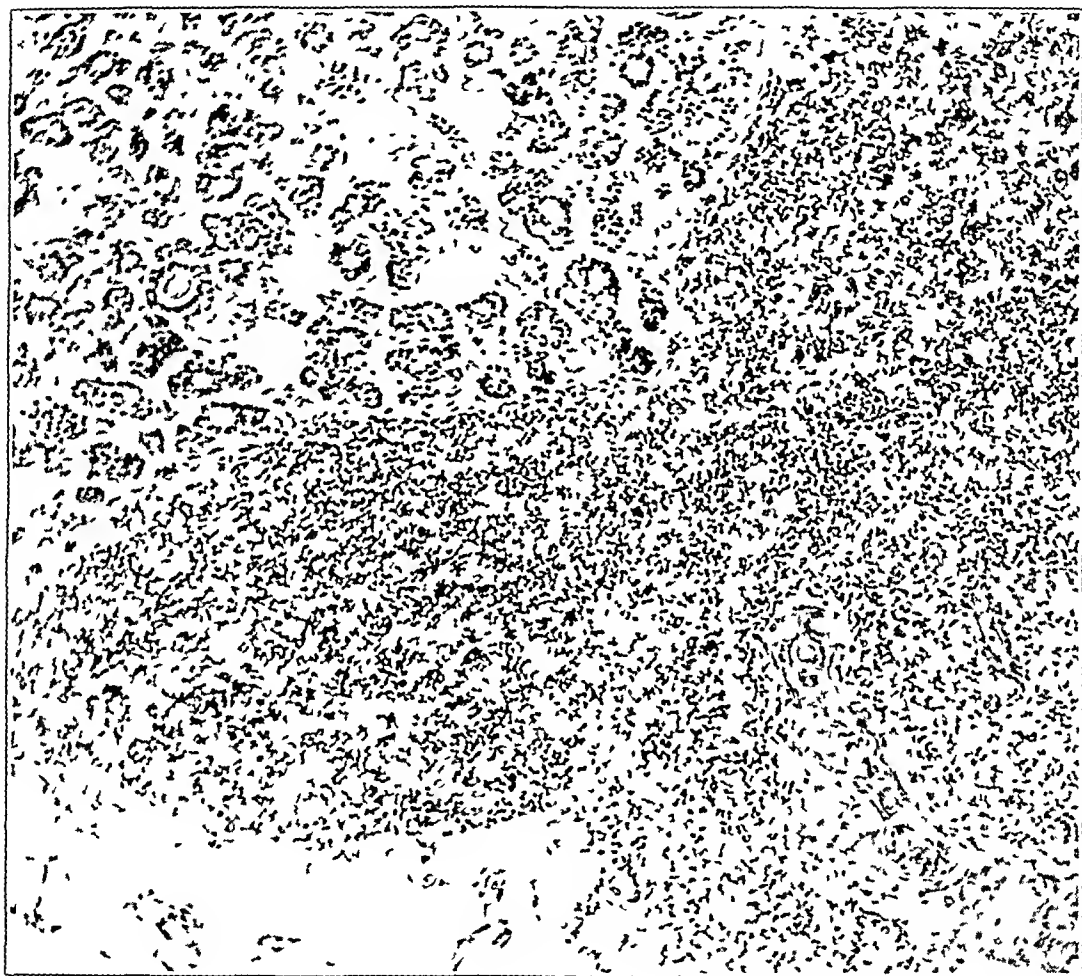


Fig 15 (case 7)—Photomicrograph of the thymus, showing the island of accessory thyroid tissue at the upper left-hand corner. A number of the thyroid acini contain colloid material. In the lower right corner, there are Hassall's corpuscles. Note the abundance of small thymic cells. Hematoxylin and eosin stains, $\times 135$.

(Streckeisen³⁸) In the dog, they are frequently found along the aorta where they may undergo goitrous enlargement, as shown by

³⁸ Streckeisen, A. Beiträge zur Morphologie der Schilddrüse. Virchows Arch f path Anat **103** 131 and 215, 1886.

Wolfer³⁹ Huttyra⁴⁰ was able to demonstrate thyroid tissue even in the heart muscle. In this case, accessory thyroid tissue was found embedded in the substance of the enlarged persistent thymus.

Thyroid tissue has also been found beneath the mucosa of the larynx or the trachea, with or without connection with the main thyroid gland lying outside. These have been found accidentally at autopsy or may have become evident through goitrous enlargements or even through carcinomatous transformation (Cappon,⁴¹ Wegelin⁴² and others). Kronlein⁴³ reported an unusual case of struma intrathoracica retrotrachealis in which the almost fist-sized struma extended down from the inferior pole of the left lobe of the thyroid into the thorax to the tracheal bifurcation between the trachea and esophagus. It markedly compressed the adjacent structures and even produced a marked scoliotic curvature of the dorsal spinal column. In Bevan's two cases⁴⁴ of mediastinal tumor, which proved to be substernal thyroid enlargement at operation, the symptomatology was mainly referable to the increased mediastinal pressure. In this case in spite of the presence of a retrosternal adenomatous goiter and an enlarged persistent thymus, the symptoms were typically those of thyrotoxicosis. The diagnosis of retrosternal thyroid becomes difficult when no toxic symptoms are present. The absence of the thyroid gland in its usual position in the neck, as in Bevan's second case, may serve to put the observer on his guard.

Quiescent retrosternal strumas can be diagnosed roentgenologically if calcium becomes deposited in degenerating, cystic, adenomatous goiters. This was shown in one of our recent cases, in which roentgen examination revealed a large calcified oval ball representing the retrosternal struma, which was later verified at autopsy (fig 16).

CASE 8—Saccular Aneurysm of the Ascending and Transverse Portions of the Aorta Simulating Mediastinal Tumor of Nonvascular Origin

J. McC., a white man, aged 43, American, married, a bookbinder, entered the medical service of Dr. Thomas Ordway on Jan. 25, 1928, complaining of cough, shortness of breath and loss of weight.

39 Wolfer, A. Die Aortendruse und der Aortenkropf, Wien med. Wchnschr. **29** 198, 1879.

40 Huttyra, quoted by von Eiselsberg, A. F. Die Krankheiten der Schilddruse, Stuttgart, Ferdinand Enke, 1901, p. 38.

41 Cappon, R. Versprengte Schilddrusenkeime in den oberen Luftwegen, Inaug. Dissert., Berlin, Aug. 14, 1911.

42 Wegelin, C. Zur Genese der intralaryngotrachealen Struma, Centralbl. f. allg. Path. **33** 73, 1922-1923.

43 Kronlein. Ueber Struma intrathoracica retrotrachealis, Deutsche Ztschr. f. Chir. **20** 93, 1884.

44 Bevan, A. D. Two Cases of Mediastinal Tumor Which Proved to Be Substernal Thyroid Enlargements, S. Clin. North America **1** 957, 1921.

Except for mumps and "rheumatic" pains on one occasion when a child, he had always been in good health. His family history was irrelevant. His wife had had four children and no miscarriages. Their oldest child had died a year previously with Pott's disease.

His present illness was of about four or five months' duration when he entered the hospital. It began with excessive coughing which gradually became worse. The coughing came in paroxysms, especially when he lay down, associated with pains in his chest and profuse perspiration. He noticed that he was becoming weaker and unable to carry on his usual amount of work. Dyspnea occurred on the slightest exertion. Anorexia was marked, and recently he had noticed difficulty in swallowing, the food seeming to stick in his throat. He expectorated a considerable amount of frothy fluid but never any blood.

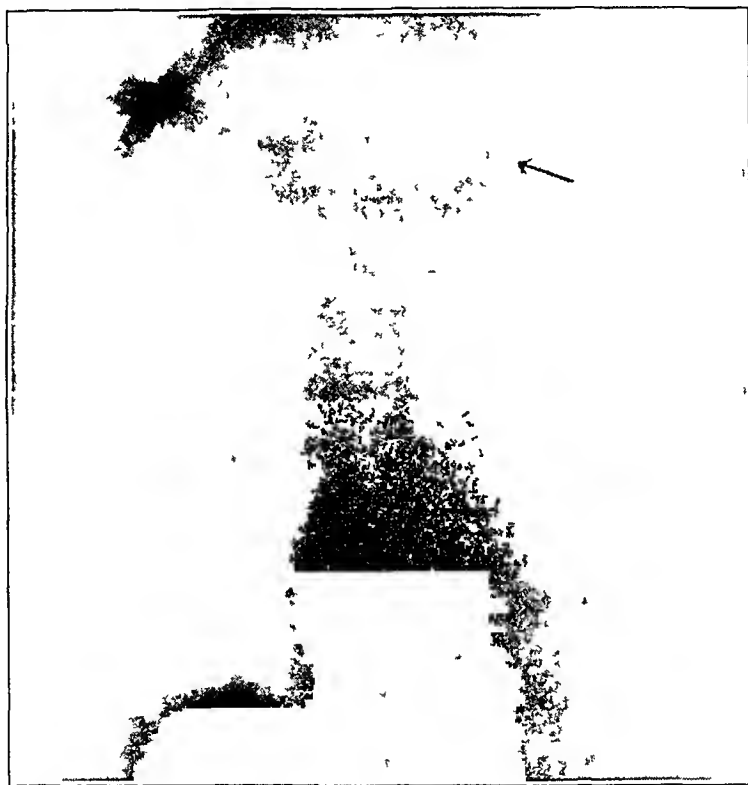


Fig 16—Roentgenogram of a patient admitted in a hypoglycemic semicoma. He had suffered from dyspnea and "asthma," with edema of the ankles, for twenty years. This plate revealed a large ovoid calcified tumor mass, 8.5 by 6.3 cm (arrow), near the left apical region, suggesting a retrosternal thyroid verified later by autopsy. The trachea is deflected toward the right.

Examination showed a poorly nourished man who had great difficulty in breathing. In his paroxysms of coughing, his face and neck became flushed from the distended blood vessels. A respiratory stridor was evident when one stood near the patient. The lips and mucous membranes were cyanotic. The teeth were in poor condition. The tonsils and pharynx were injected, and some exudate was present. No cervical or suprasternal lymph nodes were palpable. The thyroid was not enlarged.

The superficial veins of the neck and the chest were prominent, owing to the great distention. Expansion was equal on both sides of the chest. An inspiratory

and expiratory thrill could be felt everywhere over the chest. The heart was not enlarged to percussion. The heart sounds were not readily audible, owing to the loud respiratory stridor. The left lung was resonant throughout. There was an area of dullness anteriorly over the right lung, extending from the apex to the third interspace and from the axilla to the sternum. Posteriorly, this area of dullness extended down to the sixth interspace and from the vertebral column to the axilla. Over both lungs, the breath sounds were replaced by a loud inspiratory and expiratory stridor, most marked in the dull areas. No râles were present. The results of the remainder of the physical examination were of no interest.

The temperature ranged between 97 and 98.6 F. The pulse rate averaged 100 and the respirations about 25 per minute. Examination of the blood showed hemoglobin, 90 per cent, red blood cells, 4,990,000, and white cells, 13,400. Urinalysis and blood chemistry gave normal results. The sputum contained acid-fast bacilli. The serologic test gave a four plus fixation of complement with both



Fig 17 (case 8) —*A*, the barium-filled esophagus is displaced toward the left. The dense superior mediastinal shadow extends from the first rib to the upper border of the fourth rib anteriorly and 6 cm to the right of the sternum. *B*, right lateral view. The barium-filled esophagus is constricted at the level of the third rib anteriorly.

the cholesterinized and the acetone-insoluble antigens. The Kahn test also showed four plus.

Roentgen examination showed a dense shadow in the mediastinum extending from the first to the upper border of the fourth rib anteriorly and 6 cm to the right of the sternum, with compression of the lung tissue at the right upper lobe (fig 17). On fluoroscopic examination, the esophagus was displaced to the left and constricted at the level of the third rib anteriorly. The whole of the esophagus was smooth and regular. The liquid barium passed down without difficulty although a small-sized capsule was arrested at the level of the third rib anteriorly. The posterior mediastinum was encroached on by the mass, but the vertebrae were intact. On stereoscopic examination, the mass previously described was seen in the anterior mediastinum. There was obliteration of the right diaphragmatic sulcus, suggesting thickened pleura or a small effusion.

The patient rapidly grew weak, and marked dyspnea developed. He died eight days after admission to the hospital.

Autopsy was performed nine hours post mortem. The clinical diagnosis was pulmonary tuberculosis, mediastinal tumor and syphilis. The right pleural cavity was obliterated by dense fibrous adhesions. There were only a few firm adhesions in the left pleural cavity. Both lungs showed active tuberculosis with cavitation.

A saccular aneurysm, nearly 10 cm in diameter, was found about 4 cm above the aortic cusps. It included the upper ascending and transverse portions of the aorta. The cavity, about 8 cm in depth, had a roughened and somewhat stretched-out wall, which was lined by laminated layers of compact thrombus material, partially filling the aneurysmal sac. In many places the aneurysmal wall showed organization of the thrombus. Microscopic examination showed a typical syphilitic mesaortitis with marked atheroma and aneurysmal thinning of the wall.

Comment—Aneurysms of the thoracic aorta may present diagnostic difficulties. They may be mistaken for tumors, and vice versa. In this case, although both the Wassermann and Kahn tests gave a four plus reaction, there were no tracheal tug, no anisocoria and no inequality in the radial pulse. Fluoroscopic examination showed no expansile pulsation of the mediastinal mass which stereoscopic study revealed to be located in the anterior mediastinum. The symptoms and signs were mainly those of pressure on the trachea, on the superior vena cava and later on the esophagus. Aneurysms generally affect the arterial circulation more than the venous, whereas in this case there was cyanosis of the mucous membranes with marked distention of the superficial veins of the neck and chest. The rapid progress (in from four to five months), cachexia and rapid loss of weight all speak for a malignant condition but the rapidity of the course may have been due to the active pulmonary tuberculosis. As pointed out by Jack and Teacher,⁴⁵ their case of mediastinal tumor (endothelioma) with definite expansile pulsation shows that rare as the exceptions may be, there is no medical axiom of universal application.

SUMMARY

1 Eight cases of different types of mediastinal tumor masses are reported.

2 There is not a single pathognomonic symptom or sign on which one can place absolute trust in the differential diagnosis of mediastinal tumors.

3 Metastasis to the central nervous system is commonly observed. Such metastasis may initiate and dominate the symptomatology. Hence, a diagnosis of primary tumor of the brain may be made in these cases.

⁴⁵ Jack, W. R., and Teacher, J. H. Case of Mediastinal Tumor with Expansile Pulsation, *Glasgow M. J.* 87:84, 1917.

4 Tuberculosis may be suspected in the very early stages because of the persistent cough due to bronchial irritation by the growing tumor mass

5 Clinical observations must be correlated with the roentgen and laboratory data. Confirmatory evidence is obtained by (*a*) examination of the sputum or pleural fluid for tumor cells, (*b*) examination of the specimen obtained by probatory puncture or through the bronchoscope and (*c*) examination of the superficial lymph nodes containing the metastasis (biopsy)

The clinical histories of the cases reported were used with the permission of Drs. A. W. Elting, T. Ordway, G. E. Beilby, L. W. Gorham and A. H. Stein, and the roentgenograms were furnished by Dr. W. P. Howard.

INFLUENCE OF VELOCITY ON THE RESPONSE TO INTRAVENOUS INJECTIONS¹

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I UNTOWARD EFFECTS OF RAPID INJECTION ("SPEED SHOCK")

The rapid intravenous introduction of pharmacologically active or inert chemicals, drugs and biologic fluids may frequently give rise to immediate and far-reaching nonspecific sequelae, at times serious, and occasionally fatal¹ This "speed shock" is a hazard to the clinician and annoys and baffles the laboratory worker (charts 1, 2, 3, 4 and 5) In this article we shall describe, localize and discuss the possible mechanism of the deleterious effects of the rapid introduction into the blood stream of relatively innocuous substances

MATERIAL AND TECHNIC

Our observations were made on anesthetized and unanesthetized animals For the work without anesthesia, dogs and rabbits were used, and the injections were made with the hand syringe The rate of injection could not be accurately mea-

¹ Submitted for publication, April 30, 1930

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1 Hanzlik, P J, and Karsner, H T Comparison of Prophylactic Effects of Atropine and Epinephrine in Anaphylactic Shock and Anaphylactoid Phenomena from Various Colloids and Arsphenamine, *J Pharmacol & Exper Therap* **14** 425 (Jan) 1920 Manwaring, W H, Brill, S, and Boyd, W H Hepatic Reactions in Anaphylaxis Hepatic Mechanical Factor in Peptone Shock, *J Immunol* **8** 121 (March) 1923 Dale, H H Histamin Shock, *J Physiol* **41** 318 (April) 1910, **52** 355 (March) 1919, **52** 361 (March) 1919 Manwaring, W H, et al Hepatic Reactions in Anaphylaxis Hepatic Anaphylatoxin, *J Immunol* **10** 575 (May) 1925 Osborne, T Principles of Therapeutics, Philadelphia, W B Saunders Company, 1921 Lewis, J Route and Rate of Absorption of Subcutaneously Injected Serum in Relation to Occurrence of Death After Injection of Antitoxic Horse Serum, *J A M A* **76** 1342 (May 14) 1921 Hanzlik, P J Basis of Allergic Phenomena, *J A M A* **82** 2001 (June 21) 1924 Karsner, H T Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928, p 966, with full bibliography Hanzlik, P J, and Karsner, H T Anaphylactoid Phenomena from Various Agents Injected Intravenously, *J Pharmacol & Exper Therap* **14** 379 (Jan) 1920, **23** 173 (April) 1924 Hanzlik, P J, De Eds, F, and Tamter, M L Blood and Symptomatic Changes Following Intravenous Injections of a Variety of Agents and Solutions, *Arch Int Med* **36** 447 (Oct) 1925

sured, but usually from 2 to 5 cc was introduced as rapidly as the plunger could be pressed. Under anesthesia, sixty-two animals (dogs, cats, rabbits and monkeys) were used. The dogs were given morphine before anesthesia. The cats, of course, received no morphine. Either a fixed anesthetic (chlorotone or sodium iso-amyl-ethyl barbituric acid) or ether was administered. In the anesthetized animals, we recorded the blood pressure from the carotid artery, and at times the respirations. Myocardiograms were also made in three of the animals (chart 12). Fluids were injected into the saphenous vein previously prepared with a cannula. When less than 5 cc was employed, the hand syringe was used and the plunger was driven home as rapidly as possible. Larger injections were made by attaching the cannula to a 25 cc buret. The fluid was permitted to run in by gravity as rapidly as it might (usually from 3 to 10 cc per minute). Except when especially mentioned in experiments planned to show the effects of the temperature of the fluids (charts 11 and 12), all the substances were introduced at room temperature.

Substances Introduced—The substances injected during the course of these experiments included

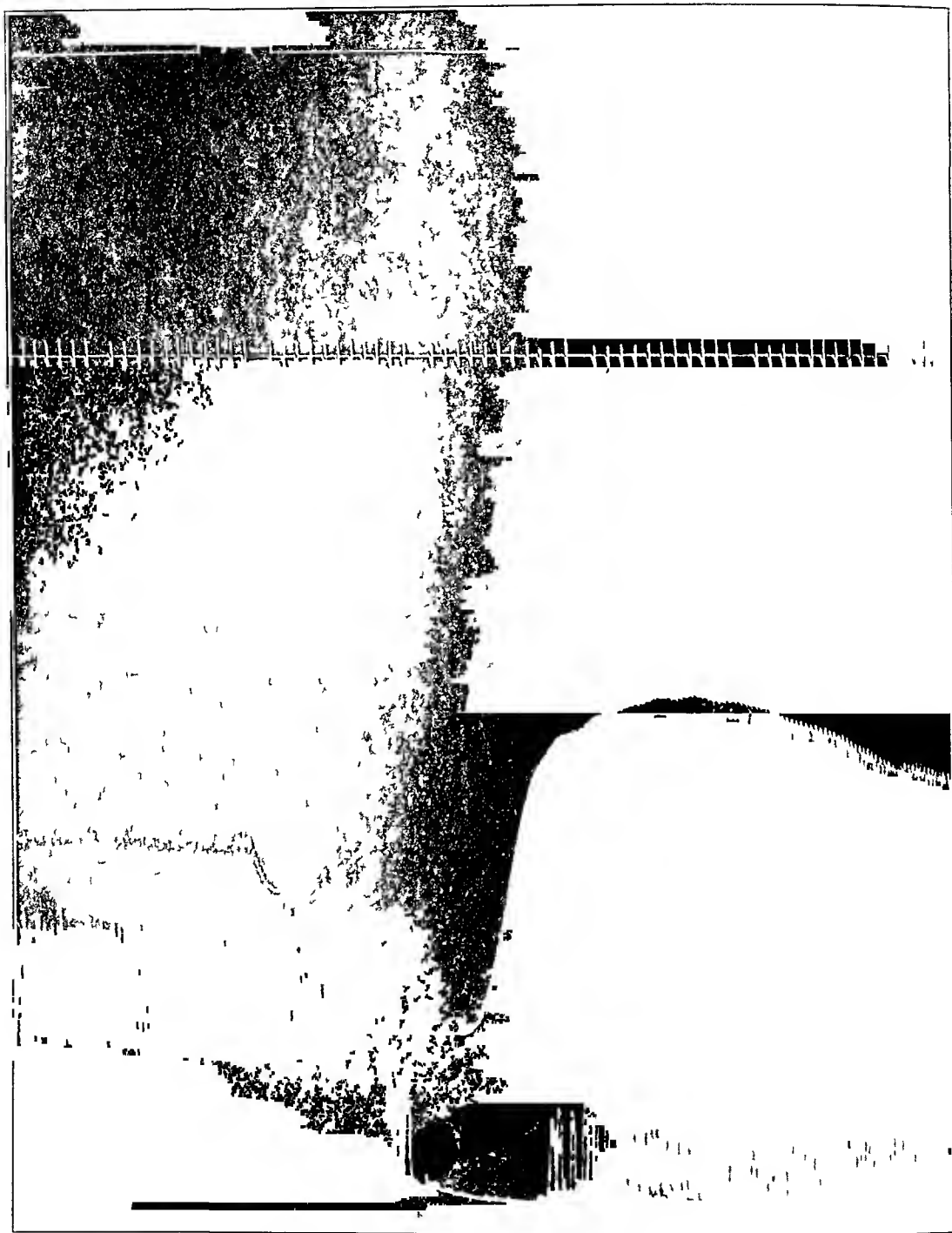
- | | |
|--|-----------------------|
| (1) Hypotonic solutions | 0.1% sodium chloride |
| (2) Isotonic solutions | 0.9% sodium chloride |
| (3) Hypertonic solutions | 10% sodium chloride |
| | 40% hexamethylenamine |
| | 20% sodium citrate |
| | 50% sodium salicylate |
| | 10% sodium salicylate |
| | 9% calcium chloride |
| | 21% sodium iodide |
| | 9% sodium bicarbonate |
| | 5% copper sulphate |
| (4) Sugars | 5% dextrose |
| (5) Colloids and gels | 50% dextrose |
| | 6% acacia |
| | 25% acacia |
| | 5% gelatin |
| | 10% peptone |
| | 0.1% agar |
| (6) Suspensions | 0.1% Fuller's earth |
| (7) Drugs (in addition to the aforementioned under hypertonic solutions), caffeine, digitalis, pituitary, nitrites, epinephrine, digitolin, digitan, histamine, strophanthin, arsphenamine, ergot, ouabain, aconitine, coramin, homocamfin, atropine and quinine | |
| (8) Biologic fluids | Blood |
| | Serum |

Plan of Experiments—In general, after waiting for the recovery of the animal from the operative procedure, we obtained a "speed shock" by rapidly introducing 1 or 2 cc of the agent under investigation (charts 1, 2, 4, 5 and 3). Occasionally, the reaction was fatal (charts 4, 5 and 3). No effort was made to resuscitate the animal. If the animal recovered spontaneously (charts 1 and 2), a slow infusion of a large amount of the same substance was introduced to eliminate the possibility that the reaction obtained might be specific to the substance or to an impurity. The shock was then reinduced by a rapid injection so that we might be convinced that the animal was still "shockable." After recovery, a second and

sometimes a third substance was injected into the animal in a similar manner, and usually, if the animal survived and was still in fair condition (which was often the case), one or more of the drugs of group 7 was employed. Each substance was tried on at least three different animals and was always used at least once on a fresh animal. In a few of the experiments we reversed the procedure and started with a slow infusion and produced shock by a subsequent rapid injection (chart 3).

CLINICAL SYMPTOMATOLOGY OF "SPEED SHOCK"

In all of our animals, irrespective of the nature of the substance injected, irrespective of the type of experiment and of all other controlled variables, we were able at one time or another to elicit in whole or in part a clinical syndrome to which we shall refer as "speed shock." The reactions occurred within from forty to sixty seconds of the injection. These included salivation, vomiting, diarrhea, dyspnea, muscle atony, or at times muscle spasm. Inconsistency and inconstancy of these symptoms was the rule. In fact, this irregularity led us to the belief that some nonspecific variable, probably velocity, was at the bottom of our inability to work out the toxicity and pharmacology of a group of pigments that we chanced to have under investigation. The major symptoms of "speed shock" consisted in changes in the blood and in circulatory and respiratory symptoms. The blood was rendered non-coagulable. We were inclined to the belief that the shock reaction preceded the blood change, and that the latter was indeed but a symptom of the former. In "speed shock," the blood pressure fell precipitously. This might be fatal (charts 3, 4 and 5), or recovery might speedily ensue (charts 1 and 2), so that the tracing at least appeared no different from the preceding strip. Coincident with the circulatory symptoms occurred respiratory distress (charts 1 and 2). There were simple dyspnea or apnea and at times collapse of the lung with a sucking in of the thoracic wall or at other times severe bronchospasm with a ballooning of the chest. Death might result from the respiratory or the circulatory accident. At autopsies, the most marked changes were usually found in the lungs, confirming the clinical observations, there was either atelectasis or emphysema. Often large fresh thrombi could be found in the pulmonary veins. Frequently multiple punctate hemorrhages were noted in the abdominal viscera. Less tempestuous fluctuations in blood pressure were also produced by altering the rate of flow within narrower limits (charts 9 and 10). An infusion made slightly too fast often caused a gentle but continuous fall of blood pressure which adjusted itself when the infusion was stopped or slowed. This reaction is probably similar in every way, except quantitatively, to the "speed shock."



Charts 1 and 2—"Speed shocks" with 20 per cent sodium citrate and spontaneous recovery. Note the fall of blood pressure (upper tracing) and two types of respiratory response (lower tracing), the one with cessation in expiration (bronchospasm with emphysema) and the other in inspiration (collapse). The time marker is in periods of five seconds in all charts.

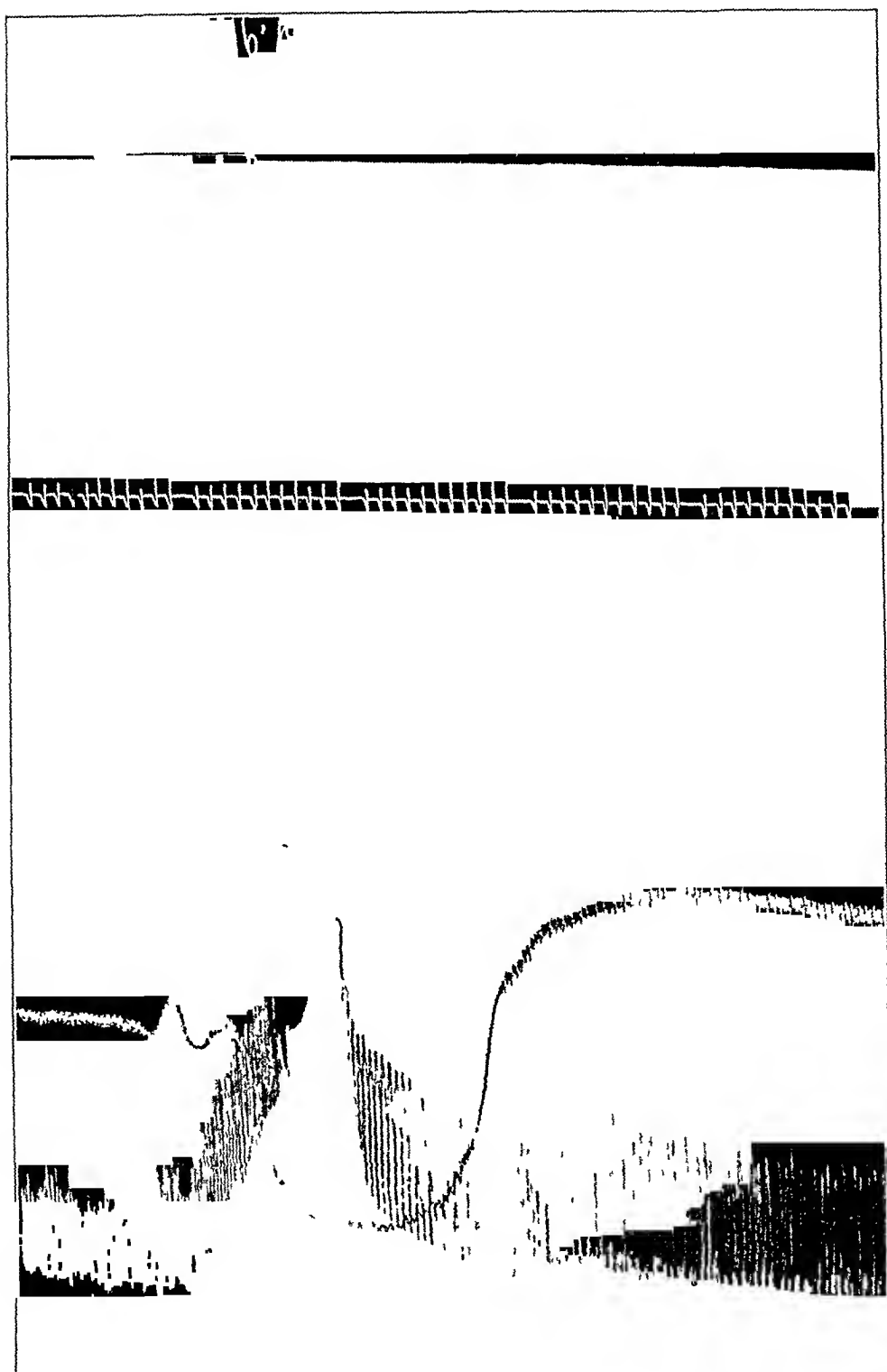


Chart 2

FACTORS THAT MODIFY "SPEED SHOCK"

The "speed shock" could not be consistently obtained with all of the substances. If an injection of 1 or 2 cc was not successful, usually a slightly greater amount of fluid (up to 5 cc) or an increase in the velocity of injection produced shock (chart 6). This was true whether we are using a comparatively inert and small molecule such as sodium

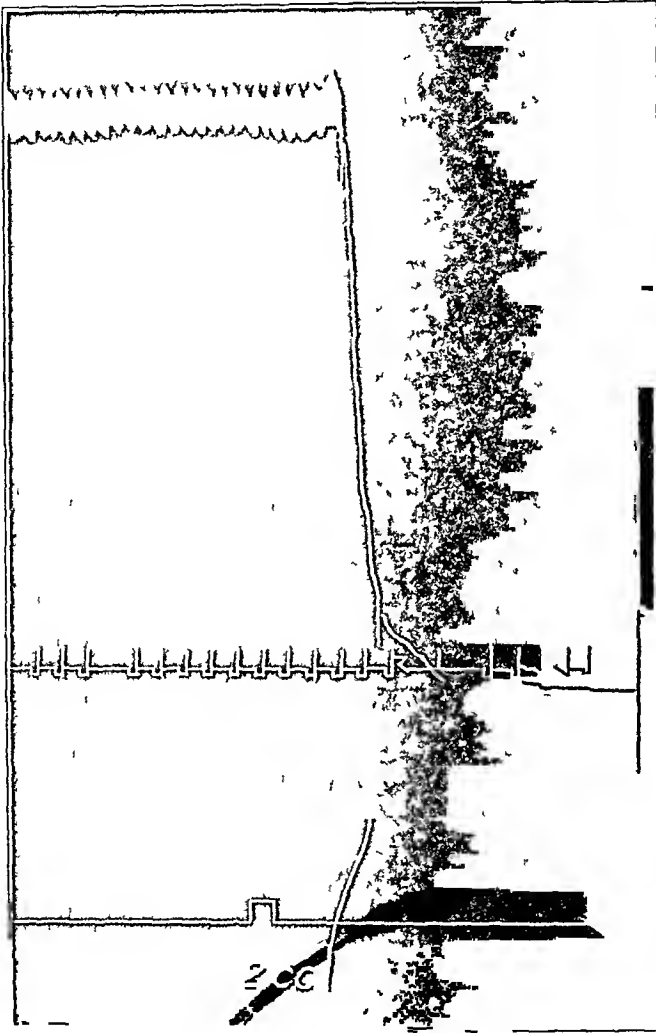


Chart 3—"Speed shock" with hypotonic solution (0.1 per cent sodium chloride). Previously the animal had received 25 cc of the same solution slowly (1 cc per minute) without any effect on the blood pressure. This illustrates how much more important is velocity than concentration, size of molecule, etc.

chloride (chart 3) or a complex molecule such as melanin (charts 4 and 5). Using 1 or at most 2 cc, we could obtain a shock regularly with 20 per cent sodium citrate (charts 1 and 2) or 10 per cent sodium chloride. In general it was easier to produce shock with the hypertonic solutions, and a large molecule was more effective than

a small one. Again, the shock seemed more readily produced with a fluid than with a viscous substance such as acacia (chart 14). The 6 per cent acacia produced shock more easily than the 25 per cent solution, despite the large number of molecules in the latter. Unfortunately, we had no way of measuring these quantitative differences. The influence of the temperature of the fluids will be discussed later.

REPEATED SHOCKS AND PROTECTION

Repeated shocks were produced with all of the substances mentioned except the sodium bicarbonate and the calcium salt (charts 6 and 12). In some cases it seemed that there was a short period in which the animal was not shockable. A certain amount of protection also seemed to occur with acacia (chart 14), and we had difficulty in producing shock by injecting into one saphenous vein while an infusion of acacia was running into the other vein.

IMPORTANCE OF OTHER VARIABLES

The production of the shock picture with so variable a list of substances pointed to the fact that the reaction must be due to some constantly present variable. Consequently, it was necessary to evaluate the importance of all other possible contributing nonspecific factors.

- 1 Species idiosyncrasy was excluded, as cats, dogs, rabbits and monkeys were used. We might add, prematurely, that identical reactions occur in man.

- 2 Morphine as a contributing cause was excluded, as it was not used in cats.

- 3 Anesthesia and anesthetics were unimportant, for we obtained the syndrome in unanesthetized animals, and in animals anesthetized with ether or with fixed anesthetics.

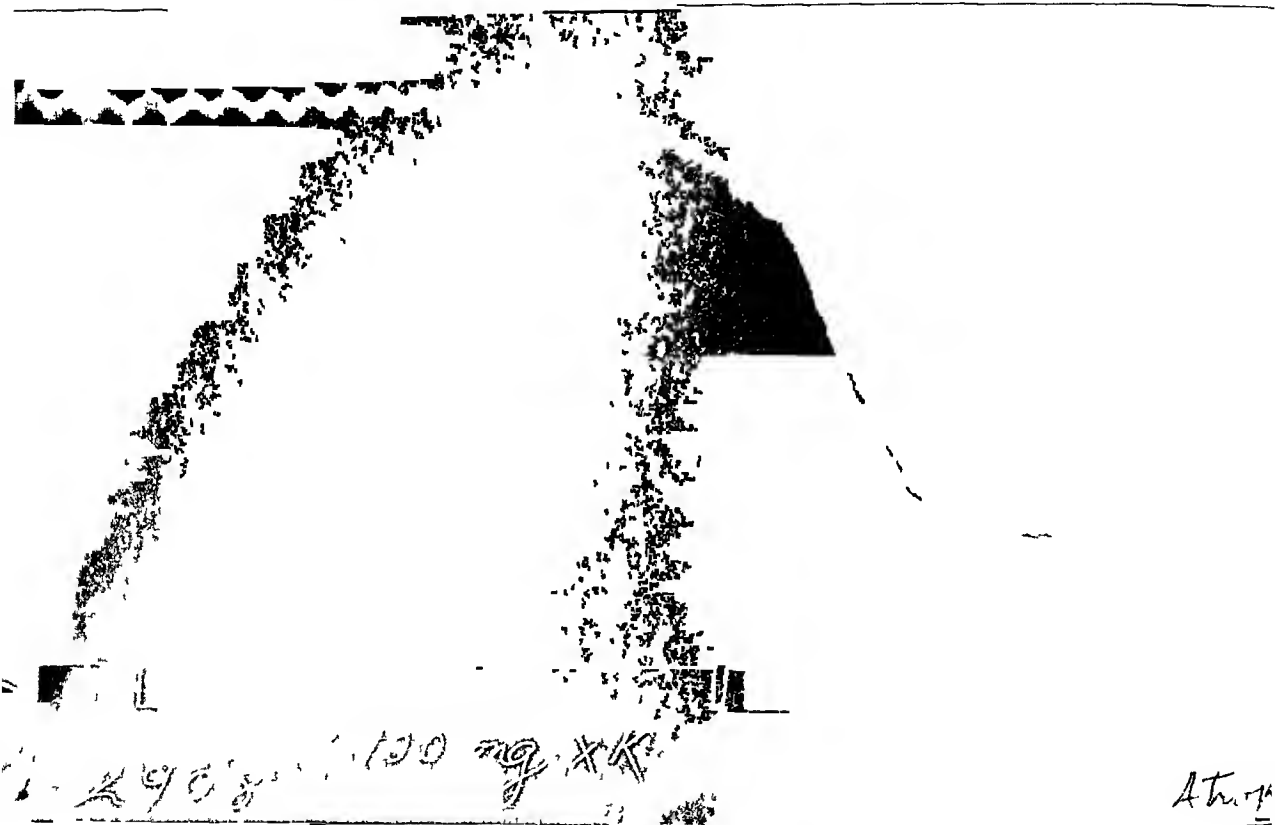
- 4 Pyrogenic substances in our laboratory diluents were excluded, for the reaction was not obtained when slow infusions were used (chart 6). Many of the agents were purchased in ampules in the open market.

- 5 The state of the circulatory system was unimportant. Shock could be produced equally well whether the blood pressure was at a normal or a subnormal level (chart 13).

- 6 The bulk of fluid injected (frequently very large) modified but did not appreciably affect the reaction. At times, with colossal amounts of fluid, such as from 10 to 20 cc per kilogram, we observed "bulk reaction." It consisted usually of a slight rise of blood pressure, a

considerable increase in the fling (pulse pressure) and some slowing in the rate of the heart

7 The temperature of the injected fluid played a minor and relatively unimportant rôle (charts 11 and 12) Usually the fluids were injected at room temperature In certain of the experiments the temperature of the fluids was carefully controlled Shock was obtained at one time or another with any given substance at any temperature whether chilled or warmed to body heat The reaction was slightly more severe perhaps when the solution was cooled or chilled The



Charts 4 and 5 — Speed shock with a complicated molecule Fatal reaction occurred with 4 cc containing 100 mg of melanin" given in ninety seconds (27 cc per minute)

thermal effect, however was slight and insignificant when compared with velocity Also, chilled solutions could be injected with impunity provided only that the rate of injection was controlled

8 The production of protein split products, such as histamine, was investigated by subjecting the fluid to dialysis The dialysates reacted exactly as the whole products or residue in the bags

9 Concentration was excluded by obtaining shock with hypotonic solutions (0.1 per cent sodium chloride) as well as more concentrated solutions (chart 3)

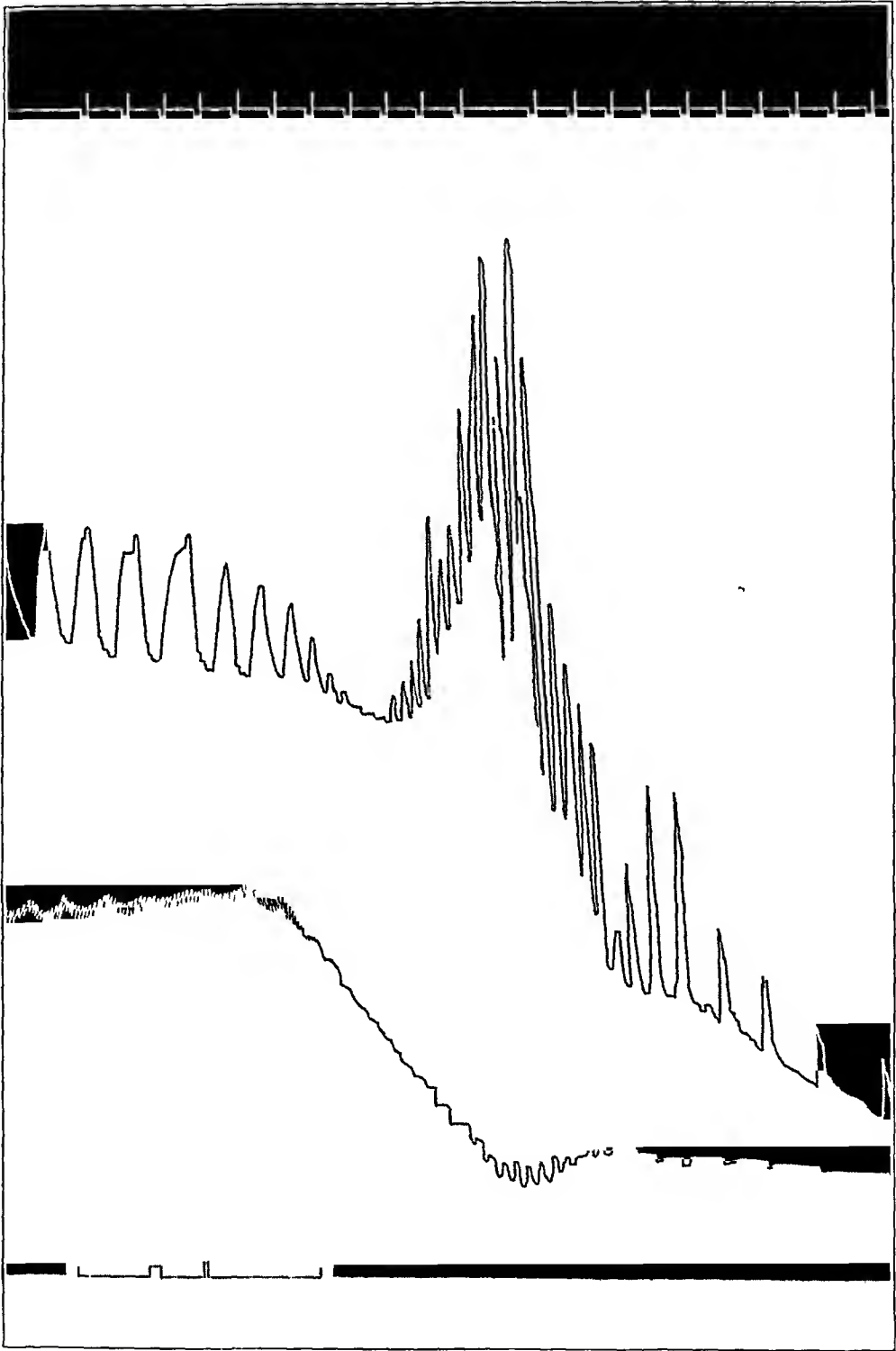


Chart 5

10 Specific effects of the agents employed could be excluded by the irregularity of results and by the harmlessness of huge slow infusions of the agent

The speed reaction that we have described is a definite phenomenon. It has previously come to the attention of other workers. Sollmann² wrote of "a primary fall in blood pressure which is apt to occur with all kinds of intravenous injections and which has been an annoying complication of experimenters on animals and no less annoying in clinical practice." In their complete report on the studies of intravenous

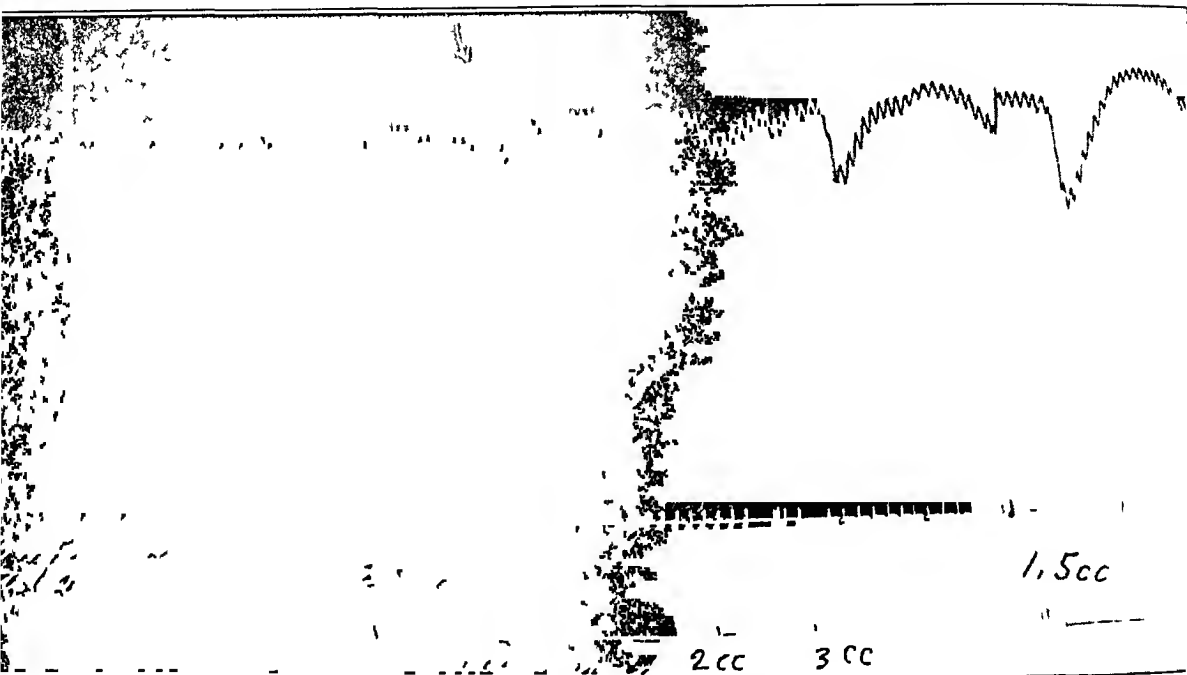


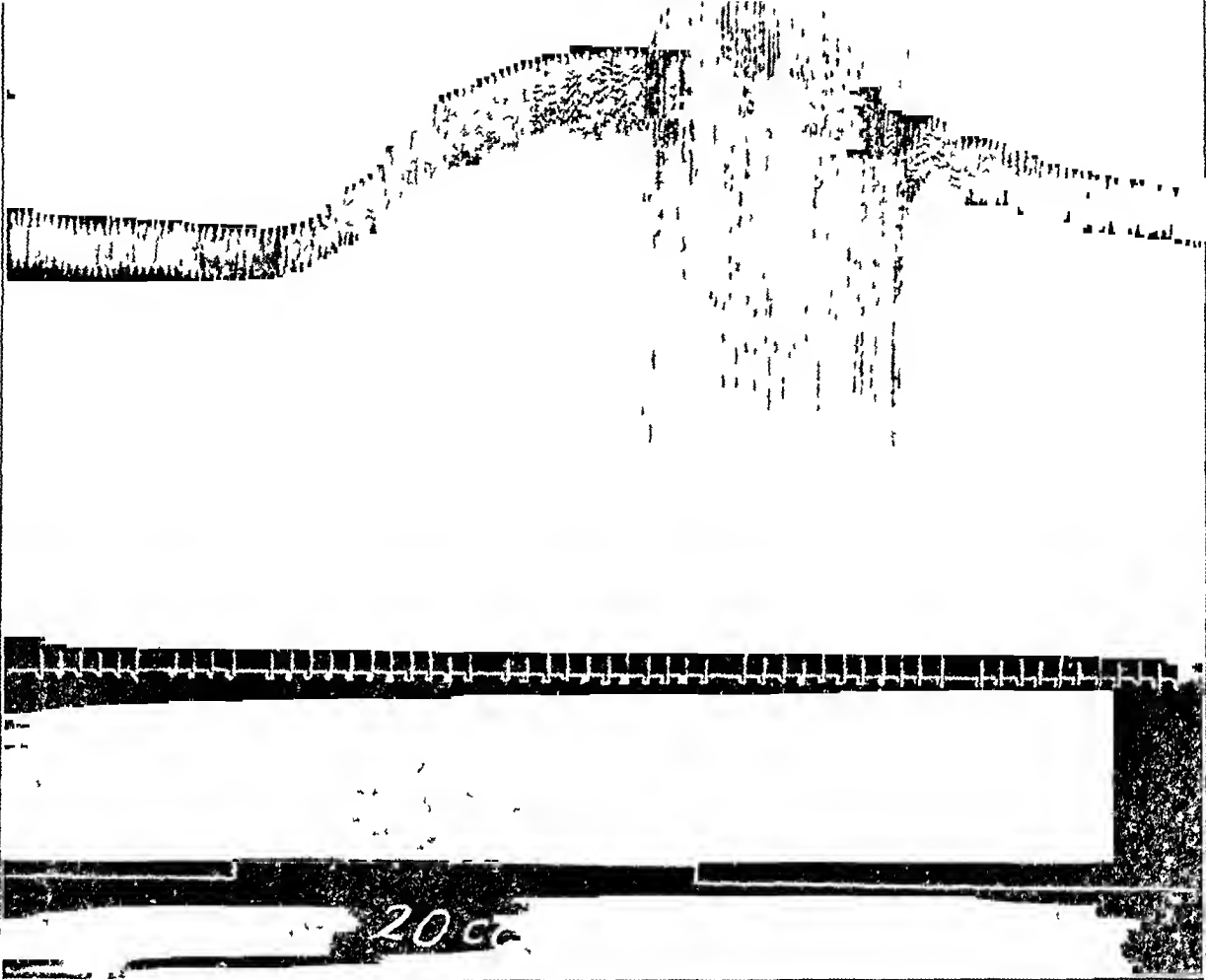
Chart 6—Between the first and second strips fifty minutes elapsed, during which time a continuous slow intravenous drip of Witte peptone (10 per cent) was administered. A total of 25 Gm in 25 cc was infused or 125 cc per kilogram of body weight or 1.25 Gm per kilogram at a rate of 1 cc per two minutes. No changes were noted until later slight shocks were obtained with 1 and 2 cc injected rapidly and marked shocks with 3 and 25 cc. This illustrates protection by slow drip, toxicity due to speed, ability to cause shock repeatedly and absence of protection.

injections the Commission appointed by the Council on Pharmacy of the American Medical Association³ said:

"The rapid administration introduces several hazards (1) the danger of overwhelming the heart and circulation with too great a

² Sollmann, T. Manual of Pharmacology, ed. 3, Philadelphia, W. B. Saunders Company, 1927, p. 73.

³ Hunt, R., McCann, W., Rowntree, L., Voegtlin, C., and Eggleston, C. Status of Intravenous Therapy, J. A. M. A. 88:1798 (June 4) 1927, 90:764 (March 10) 1928, 91:1372 (Nov. 3) 1928, 92:2099 (June 22) 1929.



Charts 7 and 8—Bulk reactions from 6 and 25 per cent acacia Note the slight effect on the systolic but the considerable fall of diastolic pressure and the increase of pulse pressure Compare with "speed shock "

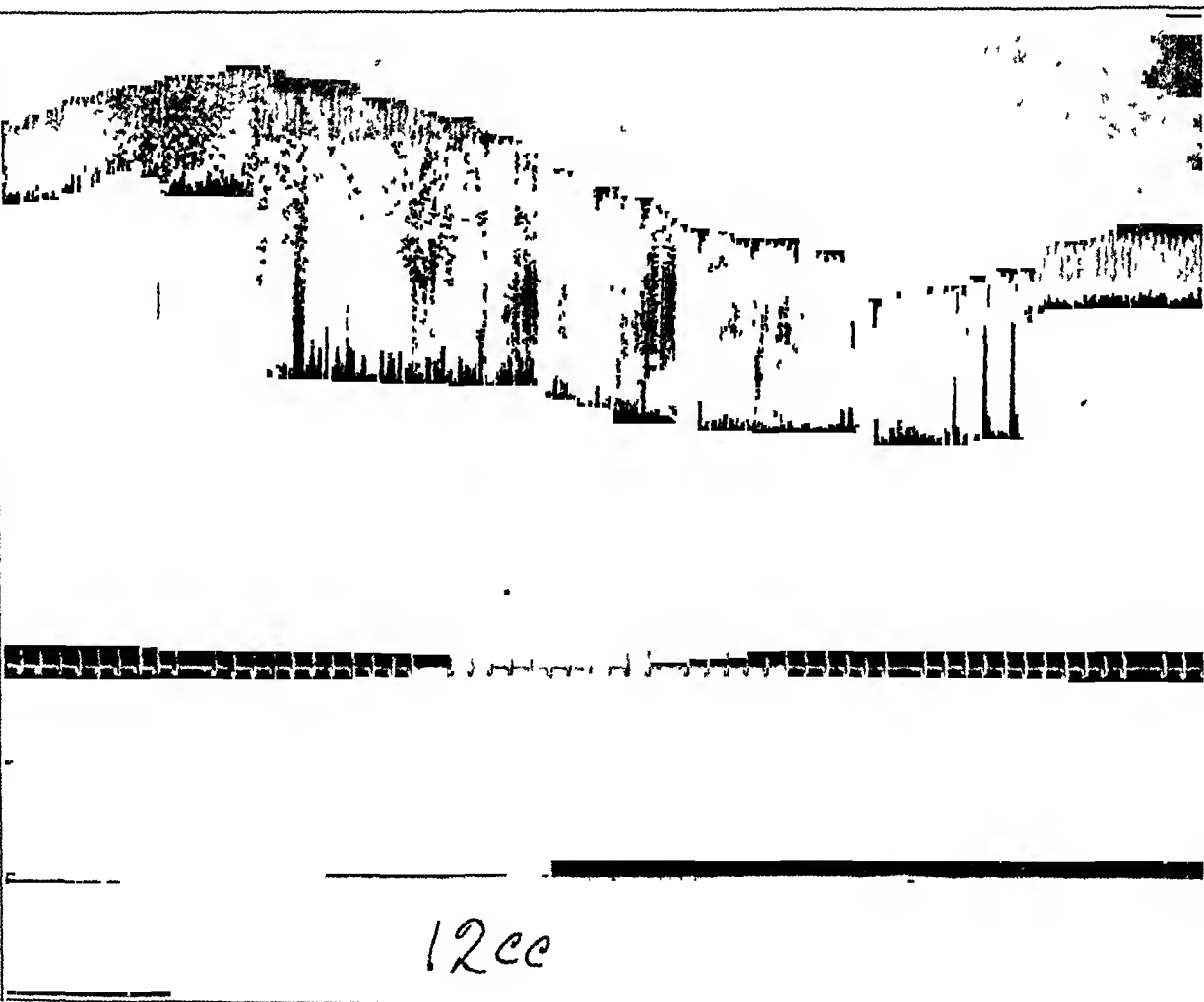
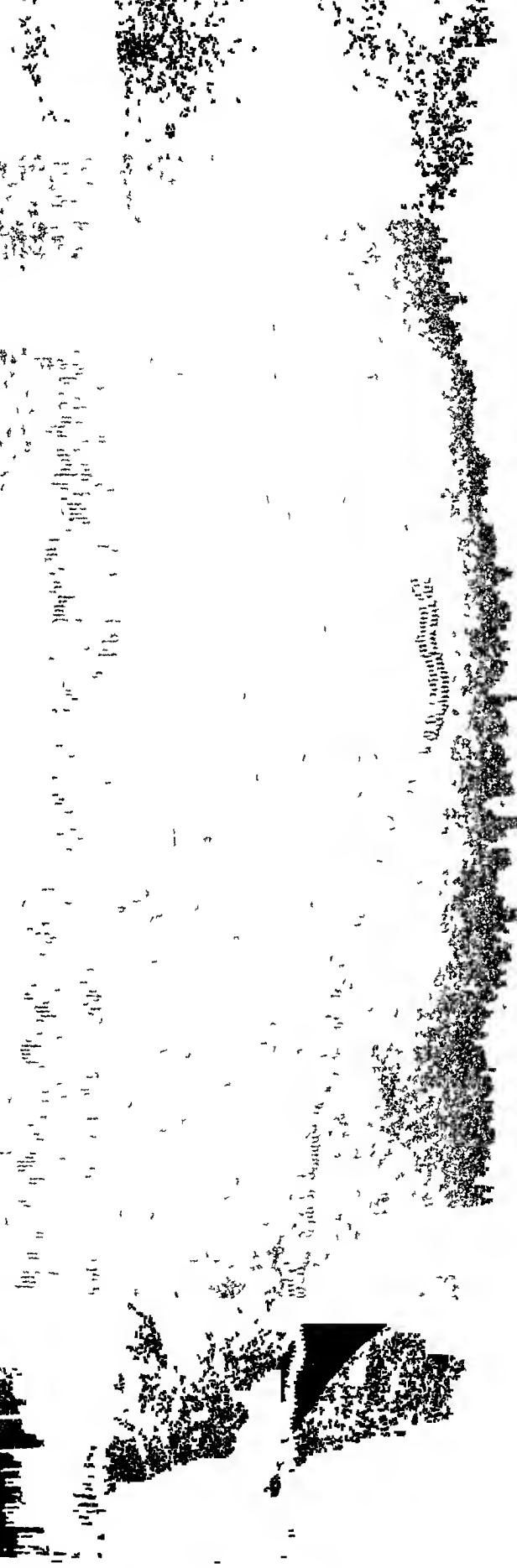


Chart 8



INJECTION
STOPPED

227 RAPID

222 — 228

14 CC

165 CC

Charts 9 and 10—Less violent speed reactions due to narrow fluctuations in the velocity of injection In chart 9, sodium chloride (10 per cent) infused at a rate of 1 cc per minute caused slight lowering of blood pressure (lower tracing) The respirations (upper tracing) were unchanged The injection was stopped and recovery followed In chart 10, recovery followed when the rate of 2 cc per minute was cut down Compare also with the bulk reaction

volume of fluid, and (2) the risk of breaking down some compensatory mechanisms as those which maintain the reaction of the blood, its osmotic tension, viscosity, and the like, within the narrow limits of normality and the likelihood of carrying the drug in too high concentration."

The first statement obviously refers to what we have described as the "bulk reaction." This, we believe, is overemphasized, and in our experience was not particularly harmful. The second statement emphasizes the role of concentration, and this, too, we believe, is relatively unimportant as compared with the rapidity with which the molecules and agents are introduced into the blood stream.

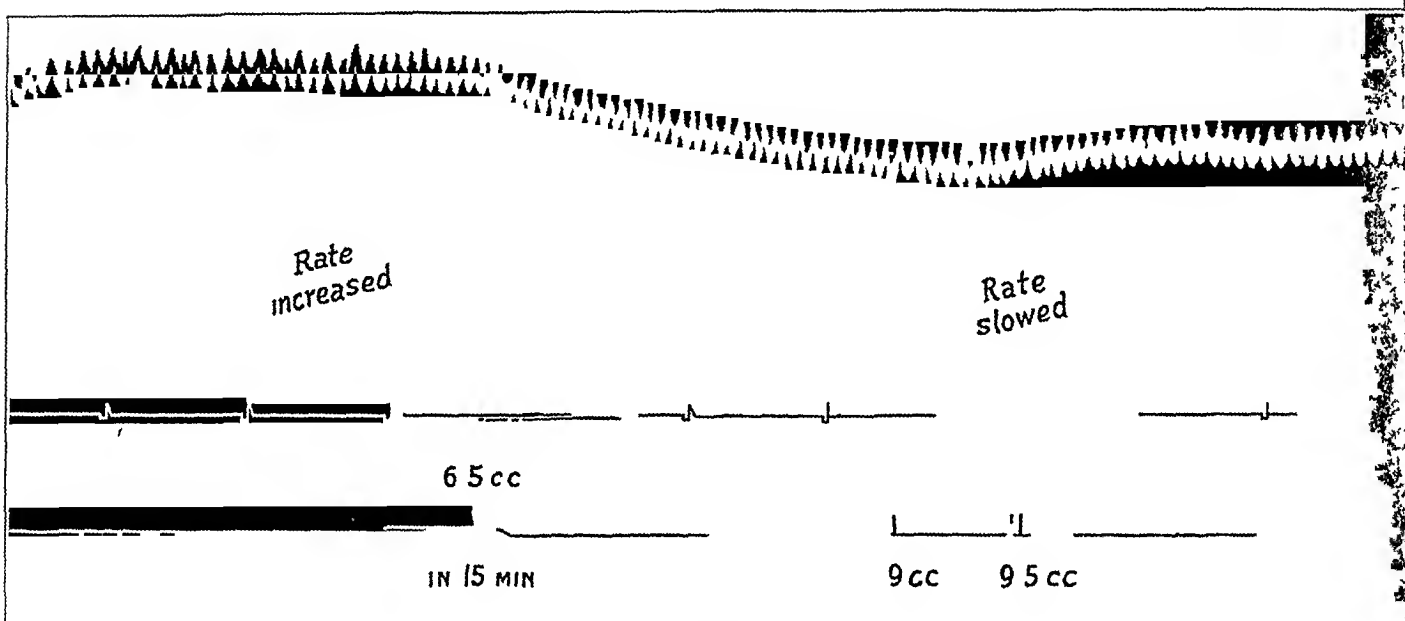


Chart 10

Further on this Committee stated that when "one considers the nicety with which these balances—physiological and physicochemical—must be preserved, the grave consequence of their disturbance and the relative ease with which they may be upset, it is truly remarkable that there are not many more serious accidents than seem to be the case."

These statements all apparently arise from a familiarity with the "speed shock" that we have described and that these other investigators apparently encountered but did not interpret. Even in his very complete textbook on pharmacology, and particularly in the section on "factors which modify intravenous injections" Sollmann⁴ did not mention velocity. The other textbooks on pharmacology are similarly silent on this point.

⁴ Sollmann (footnote 2, p. 82)

LOCALIZATION OF THE SITE OF "SPEED SHOCK"

The localization of the site of the production of the reaction was our next concern. At one time we were of the opinion that (a) some acute chemical disturbance occurred either in the hydrogen ion concentration or of the anions and cations of the blood. Loeb,⁵ who has studied this problem, looked over our work and assured us that the speed with which this reaction was experienced eliminated the possibility that the disturbance was in these spheres and dissuaded us from any chemical studies. This seemed particularly reasonable, because we obtained the

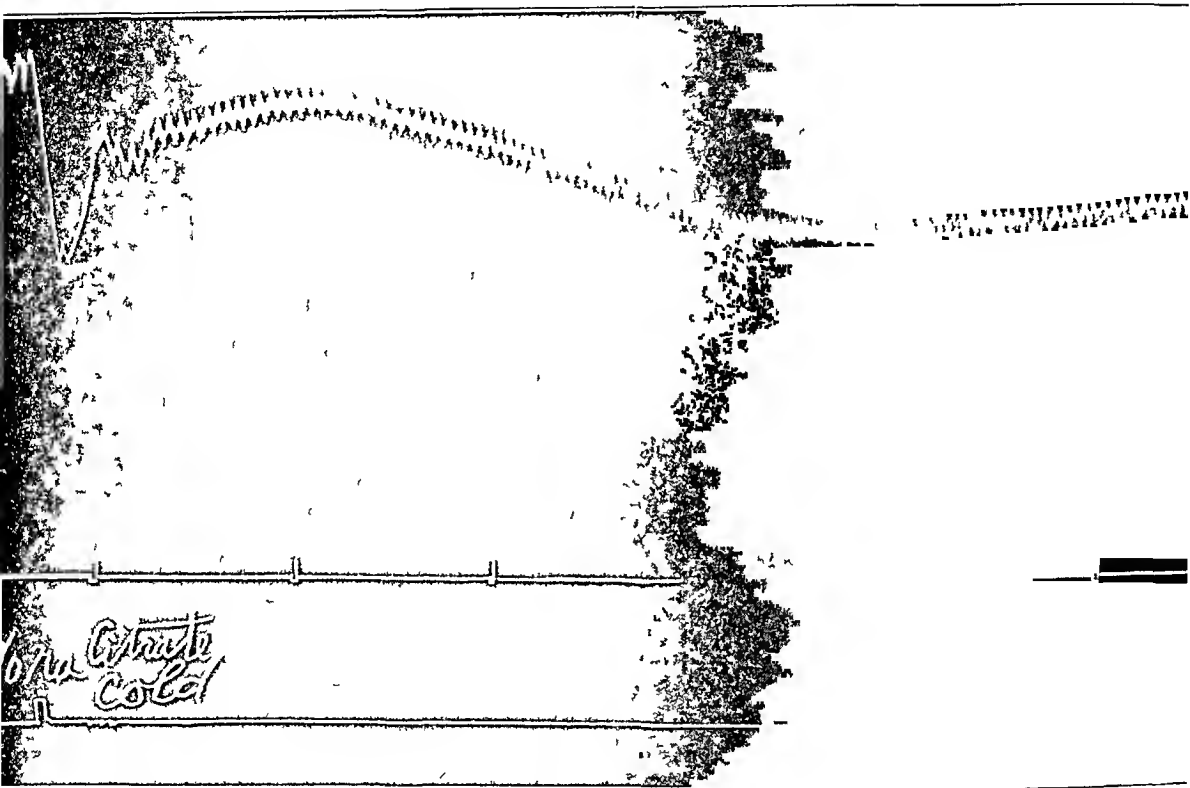


Chart 11—Left

Charts 11 and 12—Thermal experiments. Note the shocks recorded when the same solution, chilled, cooled and at body temperature was used. Note in one experiment that shock was obtained with blood pressure at 30 mm of mercury, showing that the condition of the circulation is not a factor. Compare the shock

shock with any of the anions or cations and irrespective of the reaction of the fluids. The appearance of the trace suggested also (b) the intervention of the vagal system (chart 3). However the reaction could be

5 Atchley, D. W., Loeb, R., Benedict, R., and Palmer, W. W. Physical and Chemical Studies of Human Blood Serum, Arch Int Med **31** 606, 611 and 616 (April) 1923.

obtained with the vagus intact or severed, and it could neither be prevented nor be modified in any way by full doses of atropine (*c*) Cardiac collapse was excluded by the myocardiograms which showed slight or secondary changes in the auricle and less in the ventricle (chart 12) The incoagulability of the blood suggested to Dr. Loeb that we might here be dealing with (*d*) a functional hepatic damage, and it was at his suggestion that we tried hepatic exclusions (chart 13) We could not produce the velocity reaction in animals when there had been a complete removal of the liver ⁶

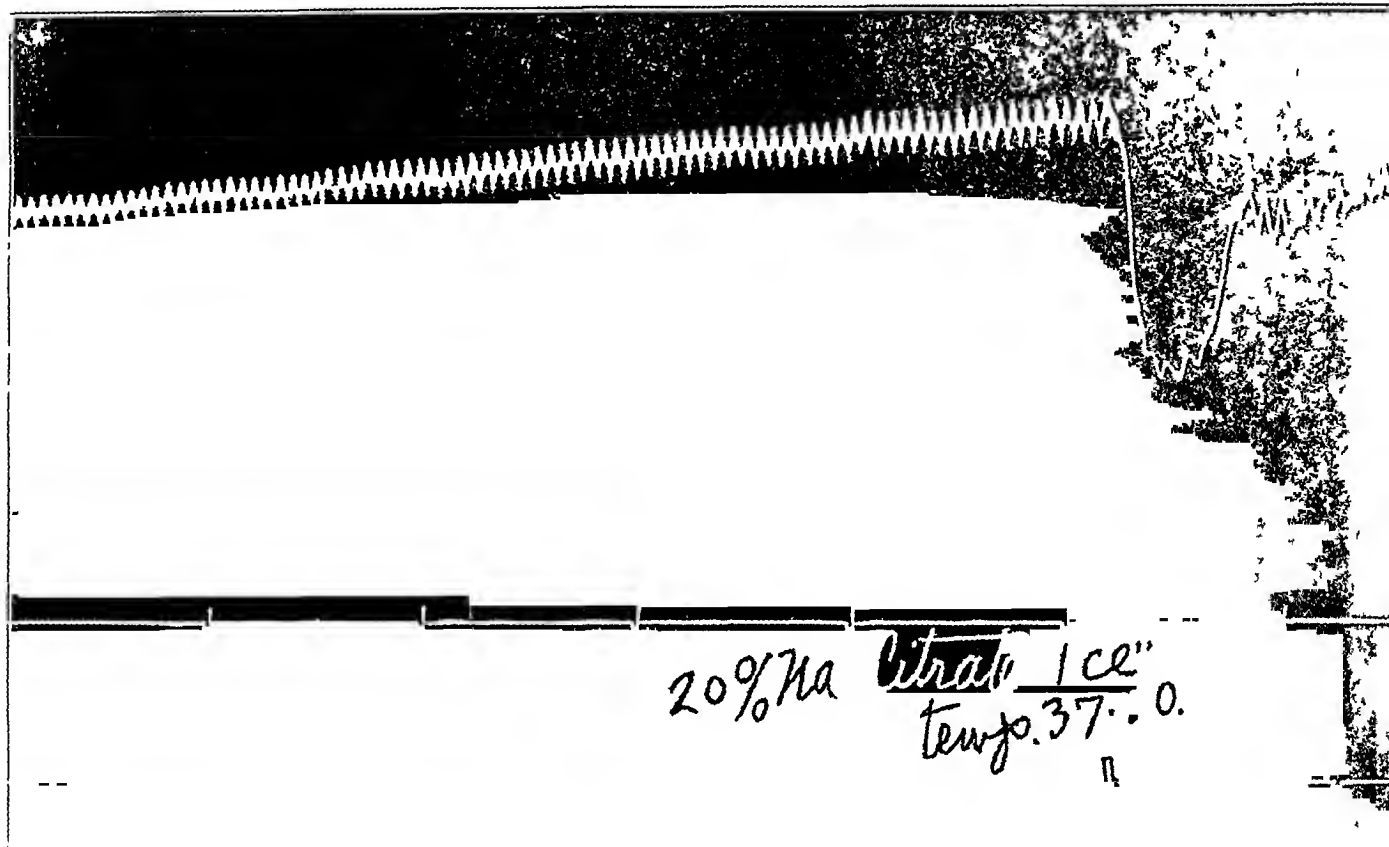


Chart 11—Right

picture with the histamine reaction, especially in chart 12 in which a simultaneous myocardiogram was made (upper tracing, auricle, middle tracing, ventricle, lower tracing, blood pressure) The changes in the heart followed the fall of pressure and were more marked in the auricle than in the ventricle The reaction is not central in origin

POSSIBLE MECHANISM

Obviously, then, the disturbances that we have described cannot occur without the intervention of the liver cell The rapidity of its development, for it followed the injection very regularly between from forty to fifty seconds, suggested that some toxic substance of the histamine ⁷

⁶ Manwaring et al (footnote 1, fourth reference)

⁷ Dale (footnote 1, third reference)

BP 30

200 Hydrocort
0.5mg

0.9% NaCl
2cc

10% NaCl
2cc

0.9% NaCl
Cold 2cc

10% NaCl
0.5cc

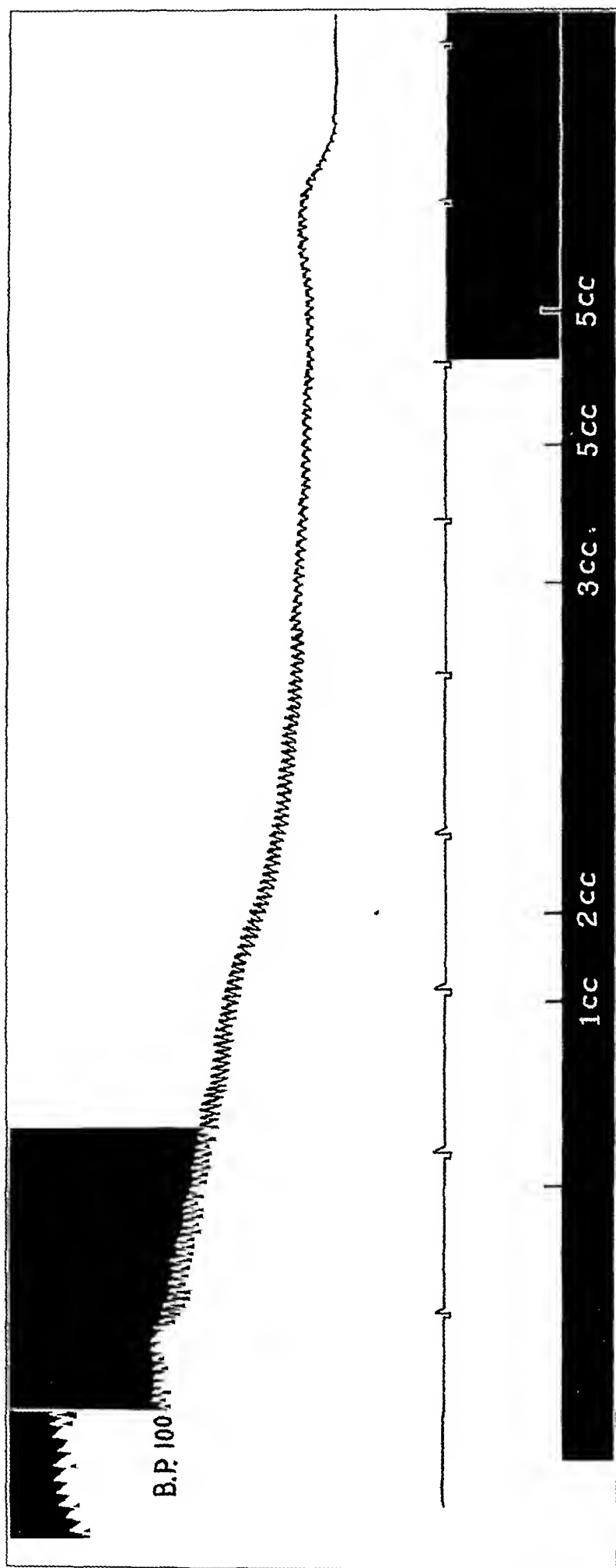


Chart 13—Complete extirpation of the liver in a dog weighing 16 Kg. The pressure was 100 at the end of the operation and fell progressively during the experiment. Shock could not be obtained with 1, 2, 3, 4 and 5 and again 5 cc of sodium chloride (10 per cent). Compare with chart 9, where shock could be obtained with pressure at 30

variety was liberated by the injured liver cell, and that the syndrome described resulted from the circulation of this substance. We attempted to demonstrate this by an experiment in which blood pressure observations were made simultaneously on two animals. In the first animal shock was produced with a rapid injection, and as the blood pressure

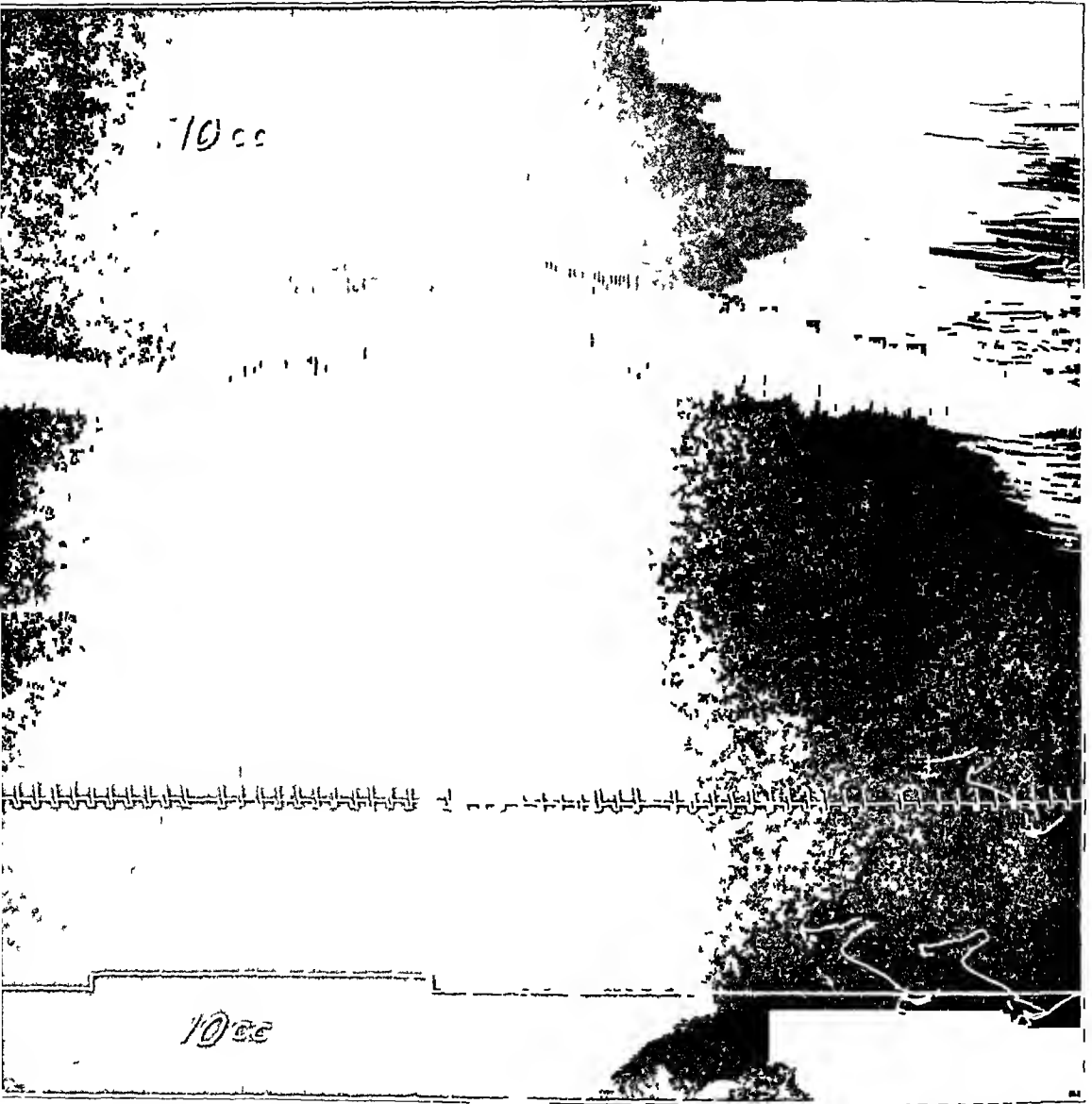


Chart 14—Acacia seems to offer some slight protection against "speed shock" After the infusion of 6 per cent acacia, shock could not be obtained even with 10 cc driven in rapidly. Note the bulk reaction, however. Later, shock could not be produced with 1 cc of sodium citrate (20 per cent)

fell 5 cc of blood was withdrawn from the heart of the animal. The blood was then slowly injected into the second animal, however, no alteration in blood pressure occurred in this animal. A similar situation is

1
1
1
1
1

1

1
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1

1
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1
1

present with the substance that produces true⁶ anaphylaxis. It too is not demonstrable in the peripheral blood though present in the blood from the ligated inferior vena cava. It is our belief that the site of action of the "speed shock" is in the liver cell. The damage to the cell obviously occurs from a physical cause—a rapid collision of molecules irrespective of their configuration or chemistry. As a result of the temporary cell damage, some potent and labile substance is liberated or escapes destruction by the liver, and this substance is responsible for the symptoms described. The toxic substance must be readily destroyed and readily formed anew. Whether or not it is histamine is a problem beyond our capabilities.

RELATIONSHIP BETWEEN "SPEED SHOCK" AND SOME SIMILAR BIOLOGIC PHENOMENA

Reaction pictures resembling "speed shock" are frequently described in the literature. A great variety of names has been applied to related if not identical phenomena: colloidoclasia, hemoclasia, anaphylactoid phenomena, etc. It is our opinion that all of these have in common an injury to the liver cell. We wish to discuss here the importance of velocity in the production of these related phenomena—particularly the anaphylactoid reaction—to inquire specifically whether or not the speed of injection is the variable at the root of all these reactions. We are reluctant to open up controversial data, but we feel the necessity of emphasizing the importance of velocity and of clearing away the multiplicity of names with their implications.

(1) *Anaphylactoid Reaction*—Of all these reactions the anaphylactoid phenomena have been most completely and painstakingly studied by Hanzlik, Karsner and their associates⁸ in a classic series of experiments. These have been summarized individually by Hanzlik⁹ and Karsner¹⁰.

These authors have furnished us with a notably complete picture of symptomatology and the alterations that occur in the chemistry of the blood. Because of the resemblance to anaphylaxis, they coined the term anaphylactoid, and they have pointed out the extreme importance of this reaction in the general field of biology and medicine because of its relationship to true anaphylaxis and other immunologic

8 Hanzlik, Karsner et al (footnote 1, first, seventh, eighth, ninth and tenth references)

9 Hanzlik (footnote 1 seventh reference)

10 Karsner (footnote 1, eighth reference)

phenomena and its close alliance to such interesting and baffling clinical phenomena as the posttransfusion chill, the nitritoid crises and reactions following the injections of foreign protein into the veins

They have concluded that¹¹ the reaction depends on the "nature of the agent used, its dose, concentration and the state of the physical functions of the animal" No mention of velocity is made in any of the articles other than to state that the injections were made through the buret at the rate of 3 cc per minute We are of the opinion that velocity was of paramount importance in their work and that the reactions were dependent slightly if at all on the "agent used, its dose concentration or the state of the physical functions of the animals" They state again that "physical and chemical changes in the blood and tissues may always be expected when agents reach the blood stream in effectual concentration and especially when introduced into the blood stream," whereas we believe this to be true only when the molecules are driven rapidly into the blood stream and untrue when the molecules are slowly introduced ("intravenous drip") even if their concentration be great

We have taken the liberty of reviewing the articles from our point of view In the most recent and complete work, fifty-six injections were made into twenty-seven dogs anesthetized with ether¹² The fluids were warmed and given slowly through the buret The rate of speed is not mentioned in this article, but in an earlier paper describing work done with guinea-pigs, a rate of 3 cc per minute was used According to the charts accompanying this paper however, the rate of injection seems to have been much more rapid Measuring from the arrow indicating the start of injection to the fall in blood pressure indicating the reaction so brief a period elapses that the fluids must have been introduced about as rapidly as was possible In chart 1,¹³ 66 cc was introduced in slightly more than one minute In the other six charts the rate seemed almost as rapid

From the published charts we find that twenty-three injections had no appreciable effect on the blood pressure, pulse or respirations (nos 12 13 and 15 with 0.9 per cent sodium chloride, no 5 with methenamine, nos 3, 15 and 18 with 10 per cent sodium chloride, nos 8 and 10 with sucrose, nos 11, 13 and 15 with dextrose, no 19 with urea, no 19 with acacia, no 20 with gelatin, no 29 with barium, no 19 with calcium chloride, no 19 with sodium bicarbonate, no 17 with citrate, nos

11 Hanzlik et al (footnote 1, seventh and tenth references)

12 Hanzlik et al (footnote 1, first and tenth references)

13 Hanzlik et al (footnote 1, tenth reference)

13 and 23 with sodium iodide, nos 17 and 20 with disodium acid phosphate), in eleven experiments the animal was in such poor condition at the time of injection that no conclusions could be drawn (nos 21 with tyrode solution, no 14 with methenamine, no 16 with urea, no 21 with sodium chloride, no 24 with agar, no 21 with horse serum no 28

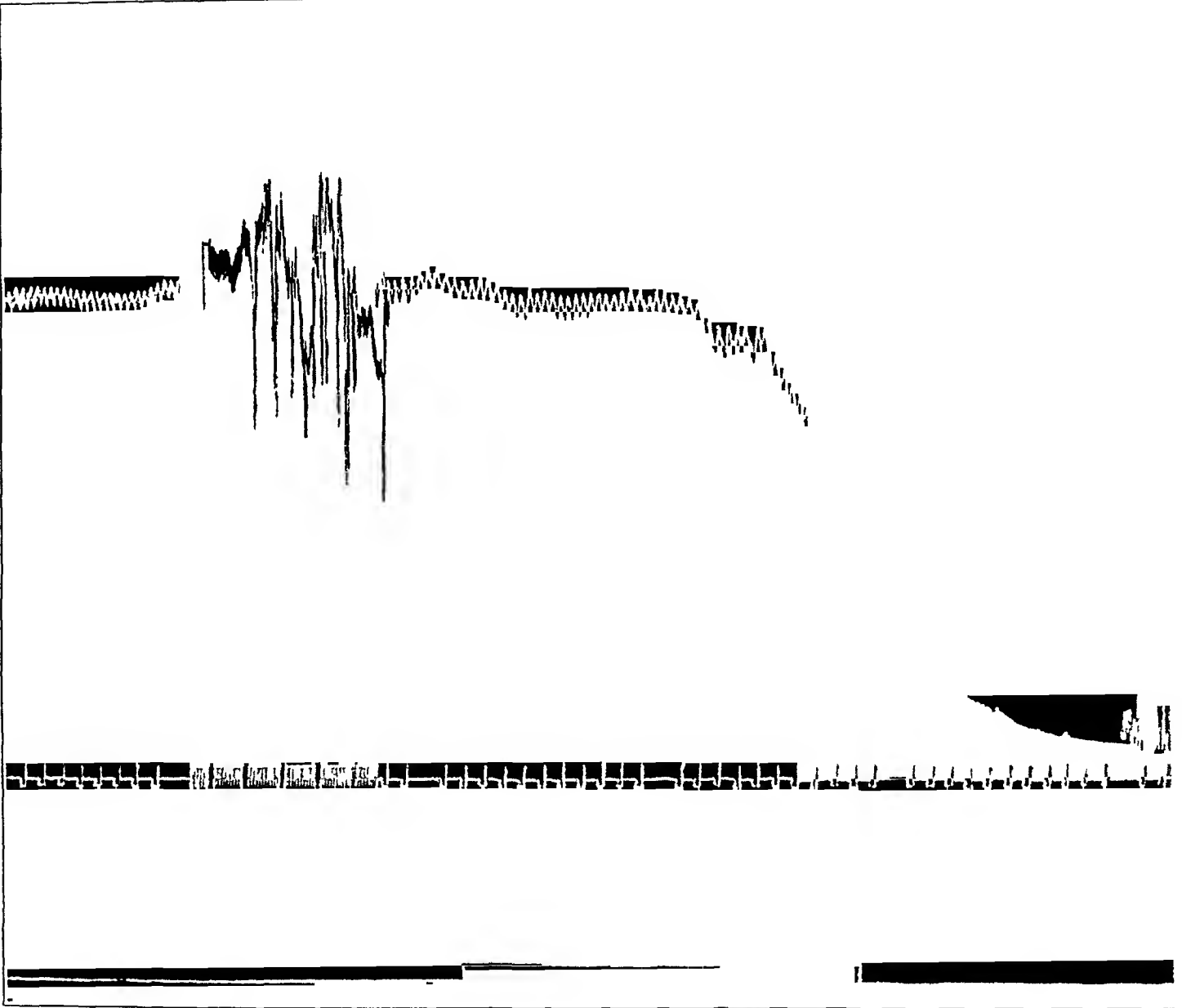


Chart 16—"Speed shock" from autotransfusion of blood At 7, 5 cc of blood was withdrawn from the heart At 8 the blood was infused rapidly through a buret into the saphenous vein of the same animal Fatal "speed shock" resulted At autopsy, the heart was still beating and there was no evidence of bleeding

with citrate, no 27 with peptone, no 16 with sodium bicarbonate, and no 22 with sodium iodide), in three animals so large a bulk of fluid had been introduced that the reaction seemed to result from volume (no 17 received 575 cc, no 20, 310 cc and no 11, 445 cc) Four animals

collapsed some time after injections apparently from a specific toxicity of the drug employed (methenamine and sodium salicylate) Fifteen animals experienced immediate reactions of the type that we have described and that these authors termed anaphylactoid (nos 25 and 26 with agar, no 14 with sodium chloride, nos 15 and 16 with methenamine, nos 18 and 23 with acacia, nos 28 and 29 with kaolin, no 18 with calcium chloride, no 32 with disodium acid phosphate, no 28 with histamine, no 28 with peptone, no 27 with asphenamine) This summary of these data excludes eleven of fifty-six experiments Of the remaining forty-five, twenty-three (52 per cent) were negative, three (7 per cent) had a bulk reaction, four (9 per cent) had a late collapse and fifteen (32 per cent) showed the reaction we are now discussing

Again, if one studies the individual agents employed, the same irregularity is observed Of four injections of saline, three gave no response and one produced shock, of five with 10 per cent sodium chloride, three produced no response and two caused convulsions, of three with agar, two caused shock and one an elevation of blood pressure, of two with calcium chloride, one produced shock and one no effect This irregularity, shown in analyses from all points of view, argues strongly against the reactions being caused by the "nature of the agent, its dose, concentration, or the state of the physical functions of the animal" We cannot possibly conceive of an interpretation of the shock reaction as due to the agent introduced, knowing full well that agar, saline, dextrose and acacia are absolutely inert *suu generis*

The use of the word anaphylactoid, we believe to be misleading Hanzlik and Karsner have themselves pointed out the differences between true anaphylaxis and the "anaphylactoid" phenomenon The latter is not necessarily caused by protein, it usually appears only on intravenous injection there is no period of incubation, there is no true and definite state of protection, hypersensitivity is not transferable, and desensitization does not occur The sole relationship to anaphylaxis as we interpret it is the fact that both cause a disturbance of the liver cell giving rise secondarily to an identical syndrome From a biologic and immunologic standpoint the reactions are wholly dissimilar

Karsner¹⁴ later indicated this when he said, "the resemblance is signified by the term 'anaphylactoid reactions or phenomena' but this does not indicate necessarily that in their essential nature they are directly related to anaphylaxis" Again he¹⁵ stated that "anaphylactoid reactions are for the most part obviously in the circulating fluids

14 Karsner (footnote 1, eighth reference, p 969)

15 Karsner (footnote 1, eighth reference, p 988)

operating secondarily on various body mechanisms, whereas the reaction in anaphylaxis is independent of changes in circulating fluids. . . . no presentation can overcome the fact that anaphylaxis is an antigen-antibody reaction and that anaphylactoid reactions are not." Hanzlik¹⁶ also stated that "whatever the ultimate explanation of the anaphylactoid reaction, the results of this paper indicate that blood and symptomatic changes occur from agents physically and chemically unrelated, some of which are relatively inert in the ordinary sense and also that more profound changes in the blood can occur than current conceptions of regulator mechanisms would indicate."

In place of the term anaphylactoid, we suggest that this syndrome be called "speed shock." This emphasizes the most potent factor in its pathogenesis, thus being of the utmost practical value and, by omission, stresses the relative unimportance of the "nature of the agent used, its dosage or concentration." It is thus a reaction based on technical error rather than a pharmacologic, chemical or immunologic entity.

(2) *Relationship to Drug Responses* —In pharmacologic studies, the "speed shock" might either serve as a constant hazard in any intravenous therapy or it might cloud studies of posology and toxicology.

(a) *Production of "Speed Shock" by Commoner Drugs Used in Therapeutic Doses* At the end of a number of our experiments, both when animals were in good condition and when they were in a state of simulating shock or collapse, we injected in therapeutic doses many of the more frequently used drugs. These were given as rapidly as possible in an effort to produce the "speed shock." At times, especially with caffeine and the digitalis bodies, a rise of blood pressure was obtained. We succeeded in obtaining typical "speed shocks" with caffeine, digitalis bodies, ergot, atropine, strychnine, quinine, arsphenamine and homocaffeine. The shocks were not regularly produced. These results served to emphasize anew the dangers of intravenous therapy, for especially in clinical emergencies, the clinician might actually produce the "speed shock" in his effort to introduce a therapeutic agent rapidly.

(b) *Velocity as a Factor in Studies of Posology and Toxicology* Studies of dosage and toxicity should take into account the factor of velocity. To take an extreme example, histamine (chart 15), though a potent vasodepressor in high concentration, when given as slowly as described previously appears to be an inert substance. The opposite error of attributing to a specific drug toxic symptoms resulting from too rapid injection is more frequent. Throughout the work of Hanzlik

16 Hanzlik (footnote 1 tenth reference p 503)

and Kaisner, previously referred to, "speed shock" symptoms are attributed to the specific agent under consideration. Without wishing to dwell again on these data, we believe that the long list of drugs and chemicals investigated by them are relatively innocuous with the exception of copper sulphate and sodium salicylate. The latter are horribly toxic. This is worthy of emphasis because of the use of sodium salicylate for injection into varicose veins. Among the substances that are quite nontoxic *sui generis*, we wish to stress hypotonic, hypertonic and isotonic saline, sodium citrate, iodide and particularly acacia. The importance of the absorption of acacia is emphasized by the controversies regarding its use clinically in shock and hemorrhage. Many report exceedingly unfavorable experiences, while others (most recently Keith at the Mayo Clinic¹⁷) are impressed with its value and have failed to encounter untoward reactions. This controversy might well be settled if the work with acacia is repeated with careful attention to velocity in the injection of the fluids. Our experiences with acacia in the laboratory lead us to believe that it may be an enormously valuable clinical adjuvant. We have found the 25 per cent solution to be less likely to cause "speed shock" than the 6 per cent. We have been able also to produce "speed shock" with asphenamine. This suggests that there might be an intimate relationship between the nitritoid crises and the "speed shock," if, indeed, these are not found to be identical. Another example of error introduced by "speed shock" is the primary fall of blood pressure resulting immediately following the intravenous administration of digitalis.¹⁸ This has been extensively studied in view of the fact that it is difficult to understand so rapid an effect from a drug that is notoriously deliberate in its dynamics. We are convinced that this is not a specific effect of digitalis, but that it is caused by overrapid introduction of the solution. This observation has extreme clinical significance in the management of emergencies which demand rapid digitalization per vein. "Speed shock" is of great significance, too, in the interpretation of the results of injection of the so-called blood pressure reducing substances, particularly those derived from the liver. Workers in these fields should particularly mention their rate of injection before discussing the specificity of the product under investigation.

(3) *Posttransfusion Reaction*—We were curious to ascertain whether the reactions following transfusion might be related to the

17 Keith, N. M. Intravenous Medication, J. A. M. A. **93** 1517 (Nov. 16) 1929.

18 Cohn, A. E., and Levy, R. Effect of Therapeutic Doses of Digitalis on the Contraction of the Heart Muscle, J. A. M. A. **74** 1597 (June 5) 1920.

“speed shock” In one experiment we withdrew 5 cc of blood from the heart of an anesthetized animal. The blood pressure and respiration were momentarily affected, and when they were normal again we rapidly infused the blood from a buret. The animal died instantly with the syndrome previously described (chart 16). The present tendency of transfusion specialists is to increase the speed of injection especially when the syringe method is employed. These studies suggest strongly the necessity of reopening the problem of posttransfusion reactions from the standpoint of consideration of the velocity of injection. Our experiences would suggest that slowly administered transfusions of citrated blood might show a complete absence of the velocity reactions, and these could easily be compared with a series of rapid injections.

(4) *Sudden Deaths Following Intravenous Injections*—In Lamson's¹⁹ report on sudden deaths, he stated that many of the deaths were “anaphylaxis-like phenomena.” No mention of velocity is made in these analyses. Similarly, in the report of Drinker and Brittingham²⁰ concerning two deaths following transfusion, all of the possible factors are analyzed except velocity. We suggest that velocity might be the unknown factor in these fatalities and that the syndrome produced might have been “speed shock.”

SUMMARY

- 1 The rapid injection into the vein of any molecule may result in widespread disturbances

- 2 This syndrome is described. The term “speed shock” is suggested.

- 3 “Speed shock” may terminate fatally.

- 4 The primary disturbance occurs in the liver cell.

- 5 The relationship between “speed shock” and the anaphylactoid reaction and other allied biologic phenomena such as the nitritoid crisis, posttransfusion reaction, etc. is discussed. The belief is expressed that these may be dependent on “speed shock.” If not, their similarity rests on their common site of origin, viz. the liver cell.

- 6 “Speed shock” is important to the pharmacologist and errata due to failure to consider the factor of velocity are illustrated.

- 7 In addition to its rôle in the foregoing conditions “speed shock” may be important to the clinician as an explanation of the sudden deaths reported following intravenous injection.

19 Lamson R W. Sudden Death Associated with Injection of Foreign Substances, J A M A **82** 1091 (April 5) 1924

20 Drinker C K and Brittingham, H H. Transfusion Reactions. Arch Int Med **23** 133 (Feb) 1919

II TOLERANCE TO SLOW INFUSIONS ("THE INTRAVENOUS DRIP")

Laboratory workers and clinicians alike recognize the importance of introducing fluids slowly into the blood stream. Friedmann²¹ reported 150 instances of patients treated with what he termed an "intravenous drip" at the rate of about 2 to 5 cc per minute. Dextrose with added epinephrine was employed. The most enthusiastic and consistent advocate of this type of therapy in this country has been Titus²². By means of an ingenious apparatus he infuses intermittently from 50 to 75 Gm of dextrose in 25 per cent solution at a rate of 4 cc per minute. He has pointed out its usefulness in toxic conditions associated especially with pregnancy. We have been unable to find any uniformity in the definition of a slow injection. According to the Committee on Intravenous Therapy³ appointed by the Council of Pharmacy of the American Medical Association, intravenous injections should always be given slowly. They quote only the figures from the workers at the Mayo Clinic who regarded a rate of from 10 to 20 cc per minute as a slow injection for water, salts and dextrose. Keith¹⁷ regarded from 30 to 40 cc a minute as a satisfactory rate of injection for dextrose. He mentioned velocity again only to state that the rate of injection of intravenous solutions is often too rapid. In Osborne's textbook on therapeutics²³ an injection of 1 quart in thirty minutes or 30 cc per minute is called a slow injection. Hanzlik and Karsner²⁴ advocated 3 cc per minute in laboratory animals.

MATERIAL AND TECHNIC

In the first section of this paper we have described the materials and methods employed in our present study. Here we shall discuss the results obtained in the same experiments, emphasizing, however, the relative innocuousness of the slow injection (intravenous drip) (charts 6 and 15) rather than the harmful effects of the speed shock (charts 1, 2, 3, 4 and 5).

The slow infusions were made through the buret. Usually a Murphy drip was placed between the tip of the buret and the vein cannula, so that we could accurately regulate the rate of flow. Attempts to use complicated automatic apparatus were early discarded. Conditions that require intravenous administration are of sufficient importance to warrant the constant presence of the experimenter or clinician. There are so many variables, such as the variation in height of the column of fluid, the patency and caliber of the tubing, vein clotting, changes in blood pressure, etc., that no piece of apparatus can be found to care

21 Friedmann, M. Ueber intravenöse Dauerinfusion, *München med. Wchnschr.* **60** 1022 (Nov.) 1913.

22 Titus, P. Apparatus for Regulating Rate of Flow and Temperature of Intravenous Injections of Dextrose and Other Solutions, *J. A. M. A.* **91** 471 (Aug. 18) 1928.

23 Osborne (footnote 1, fifth reference).

24 Hanzlik and Karsner, in Sollmann (footnote 2, p. 380).

for all the exigencies that arise. We wish to emphasize again that our solutions were injected at room temperature. This was a deliberate measure on our part to accentuate the importance of velocity in the continuous slow injection. The chart appended presents data on the tremendous quantities of fluid bulk and substances that we were able to introduce into the blood stream under these conditions with absolute impunity and without altering the blood pressure. It is in striking contrast to the serious and often fatal reactions that were obtained in using the same substances in small amounts but given rapidly into the blood stream.

MODIFICATION OF CONCEPTION OF SPECIFIC TOXICITY

These figures demand a new definition of "specific toxicity" of substances. The degree to which slow infusion may modify conceptions of toxicity is best illustrated by a remarkable experiment (chart 15) with histamine.¹⁹ Twenty-seven cubic centimeters of histamine (1 per cent)

Effects of Slow Infusions

Experiment	Weight of Animal, Kg	Agent	Solution, per Cent	Total, Ce	Ce per Kg	Total, Gm	Gm per Kg	Ce per Min
26	2.3	NaCl	10.0	23.0	10.0	2.3	1.0	1.0
50	2.4	NaHCO ₃	9.0	48.0	20.0	4.3	1.8	1.0
13	2.5	Na citrate	20.0	9.2	3.7	1.85	0.74	Intermittently
29	2.3	Na citrate	20.0	16.3	7.1	3.3	1.43	0.2
49	2.2	NaI	21.7	22.0	10.0	4.8	2.2	1.0
49	2.2	CaCl ₂	9.0	22.0	10.0	2.0	0.9	1.0
50	2.7	Menthenamine	40.0	32.0	12.0	13.5	5.0	Intermittently
25	3.5	Menthenamine	40.0	55.0	15.0	22.0	6.3	2.0
26	3.1	Dextrose	50.0	125.0	40.0	62.5	20.0	1.0
33	3.75	Acacia	6.0	98.0	26.0	10.0	2.7	1.0
48	3.8	Acacia	25.0	61.0	16.0	15.2	4.0	0.7
34	2.0	Peptone	10.0	25.0	12.5	2.5	1.25	0.5
27	2.6	Agar	0.1	13.0	5.0	0.13	0.05	0.1
31	2.7	Histamine	0.01	27.0	10.0	0.0027	0.001	0.25
40	3.0	Gelatin	5.0	30.0	10.0	1.5	0.5	0.3

(1 cc equals 0.1 mg) was infused slowly and continuously over a period of one hundred minutes (1 cc in four minutes). The blood pressure of the animal was higher at the end than at the beginning of the infusion. The respirations were unaffected. The only variations were due to pinching the rubber tubing in order to accelerate the flow occasionally. Each of these pinches was accompanied by a marked fall in blood pressure, verifying the potency of the drug. In another experiment, 10 cc of horse serum was infused slowly into guinea-pigs sensitized ten days previously. No evidences of anaphylaxis occurred. Later 0.1 cc was injected rapidly, and the animals died of typical shock. These two experiments emphasize the importance of velocity in producing changes in concentration sufficient to negate the reaction of labile but potent substances. Infused under the circumstances described that threshold value could not be reached for the rate of disappearance of the histamine must have at least equaled the intake.

Toxicity figures are also open to criticism when the nonspecific symptoms of speed shock have been attributed to inert agents employed rather than to the technical error of too rapid injection. Thus Hanzlik and Kaisner speak of the toxicity of hexamethylenamine, agar, peptone Fuller's earth, hypotonic and hypertonic saline, acacia, etc., whereas the symptoms produced are nonspecific and, unlike the histamine, not cumulative, unrelated to threshold value or concentration and are due wholly to the speed of injection.

NECESSITY OF STANDARDIZING VELOCITY

The velocity of injection should be standardized both in the laboratory and in the clinic. We do not believe that any single rate can cover all drugs. For obviously hypertonic solutions should be given slower than isotonic and large molecules slower than small molecules. Again, inert substances (saline, dextrose and acacia) may be given more rapidly than slightly active substances such as methenamine or arsphenamine. These in turn can be given more rapidly than potent substances such as histamine, epinephrine, etc. Toxic substances such as copper sulphate, etc. must be given intermittently as well as slowly if they are to be given at all. An ideal rate would be one that eliminated the possibility of speed shock and yet permitted the drug or agent to reach its threshold value and give its specific effect. We suggest that in pharmacologic assays, at least, a rate of 1 cc per minute should be accepted as standard. In the clinic this rate would be impracticable for an infusion of 500 cc. would take eight or ten hours to complete. For clinical purposes, 2 or 3 cc. should be the upper limit for amounts of over 100 cc. and 1 cc. a minute for smaller amounts. These figures should not be regarded as the last word, but are to be regarded as a first attempt to standardize the velocity of intravenous injections.

POSSIBLE CLINICAL VALUE OF INTRAVENOUS DRIPS

With slow infusions (intravenous drips) such as we have described, it may be possible to give much larger quantities of useful substances (acacia, dextrose, methenamine, serums, etc.) without the hazard of the nonspecific speed shock reactions or even of true anaphylaxis. The huge amounts of fluid that can be handled in this way also demonstrate the extraordinary equilibratory mechanism in the body for handling fluid. The bulk reaction is easily recognizable and not dangerous. It may be abolished by intermittent infusion or a slow rate. The possibility of applying these suggestions to the treatment for shock and

hemorrhage and in serum therapy is especially suggestive. We suggest to clinicians who may be interested to follow these suggestions that the vein be exposed and a large sized cannula tied in with ligatures. The fluids may be run in from a buret or reservoir and need not necessarily be heated. An electric pad wrapped around the terminal rubber tubing may be an added protection. It is conceivable that such an intravenous drip will prevent "speed shock," anaphylactoid reactions, nitritoid and hemoclastic crisis, posttransfusion reactions, peptone shock and the sudden deaths,²⁵ described as following intravenous injections. It is not even too much to hope that the true anaphylaxis²⁶ may be avoided.

SUMMARY

1 A slow intravenous drip permits of the introduction of huge quantities of fluid and agents of all sorts.

2 Even toxic products may be introduced with impunity, especially if the injection is interrupted.

3 The practical value of these observations in the prevention of "speed shock," anaphylaxis, anaphylactoid and allied biologic reactions is discussed.

Throughout these studies we have had the constant aid of Prof. Charles C. Lieb.

25 Hanzlik and Karsner (footnote 1, first reference)

26 Lewis (footnote 1, sixth reference)

REACTIONS FOLLOWING TRANSFUSION OF BLOOD, WITH URINARY SUPPRESSION AND UREMIA *

JAMES BORDLEY, III, M D

PHILADELPHIA

INTRODUCTION

For more than 250 years those who have attempted to restore health by the transference of blood from a normal to a diseased person have been keenly aware of certain attending dangers. As early as 1667, Jean Baptiste Denys described in vivid style ¹ the outstanding features of the so-called hemolytic transfusion reaction, which until recently served as an inexplicable and insuperable barrier to the transfusion of blood. An understanding of the nature of the incompatibilities that are responsible for these frequently fatal reactions came only after the studies of Landsteiner ² on hemagglutination in 1901, a simple method for determining compatibility grew out of the classifications of Jansky (1907) and Moss (1910). As a result of these discoveries, transfusion of blood became a popular therapeutic procedure at about the time of the World War, today, provided one has taken the necessary precautions in preliminary grouping and cross-agglutination tests, it is a procedure relatively free from danger. Nevertheless, transfusion reactions still occur, and although some of them are undoubtedly due to carelessness in the preliminary steps, it has been learned that certain reactions, most of them mild but others severe and fatal, cannot be clearly explained on the basis of the obvious incompatibilities discovered by Jansky and Moss.

In order to separate the unimportant from the serious transfusion reactions, recent authors have made an effort to formulate a classification of the various types. The classifications are for the most part symptomatologic, and are designed for the guidance of the operator of the transfusion, they deal primarily with the occurrences during and immediately following the injection of blood, they distinguish the trivial incidents from the danger signs. Three broad types of reaction are set forth: the "incompatible," the "citrate" and the "allergic." The

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1 Denys' patient, after a severe immediate reaction with paresthesia, sweating, lumbar pain, smothering sensations and vomiting, "fell asleep about 10 o'clock." The next morning he seemed improved and "made a great glass full of urine, of a color as black as if it had been mixed with the soot of chimneys" (Keynes, Geoffrey. Blood Transfusion, New York, Oxford University Press 1922)

2 Landsteiner, K. Ueber Agglutinationserscheinungen normalen menschlichen Blutes, Wien klin Wchnschr **14** 1132, 1901

names would imply that the classification is etiologic, but the etiology cannot be well established except for the first of the three. The type of reaction originally described so well by Denys is the "incompatible", it is nearly always associated with agglutination or hemolysis of the donor's cells by the recipient's serum, in many cases, it will prove fatal unless the early manifestations are observed by the operator. The "citrate" reaction is generally characterized by a still unexplained slightly delayed febrile response, it is a common enough reaction even when the blood is given without the citrate and it fortunately seems harmless. "Allergic" reactions may take the form of urticaria, asthma, localized edema, severe shock or some other phenomenon belonging to the allergic group. Certain other less common reactions do not fall readily into any orderly arrangement.

This classification of transfusion reactions is inadequate in one important respect. It does not tell the complete story of the reacting recipient. One is left to wonder what happens to the person who receives blood that is not suited to his circulation and who, nevertheless, does not die immediately. Does he always void "a great glass full" of sooty urine and then go on to a speedy recovery? Does he remain ill for some time and recover by slow stages? Does he linger on and die days or weeks later? A partial answer to these questions will be found in this paper, which presents a number of cases in which the reactions following the transfusion were greatly prolonged or delayed for several days.

The subject of delayed reactions following transfusion is not entirely new, a number of clinical and pathologic details have been outlined in case reports by various authors. Just where these prolonged or delayed reactions fall into the common classifications it is difficult to say. From the available data one is led to believe that most of them, perhaps all, are due to the use of demonstrably incompatible blood. Many of them originated with the classic reaction of Denys. Whether or not they all belong to the same etiologic group, they certainly have many points in common, and the outstanding feature is nearly always urinary suppression with uremia. When it is realized that a large proportion of the serious reactions that have been reported since 1924 are of this delayed type, the matter seems well worth review.

In the following pages, a detailed description will be found of three cases that were seen by the staff of Johns Hopkins Hospital and that are reported for the first time^{2a}. For purposes of comparison

2a Of these three cases I saw only case 1. The clinical observations on cases 2 and 3 were made by other members of the hospital staff to whom I am indebted for many of the data presented in the succeeding parts of this paper. Dr. Warfield T. Longcope was responsible for focusing our attention on the transfusion when case 1 first showed signs of uremia, and his very full notes on case 2 made it possible to trace accurately the various clinical events after a lapse of six years.

and study, fourteen other cases have been gathered from the literature and are presented in tabulated form. Space will not allow a full abstract of the cases of other authors, but those who care to refer to the original descriptions cannot fail to be struck by the similarity of the clinical course in almost all of them. Brief mention is made of several cases that undoubtedly belong to this group, but of which the available descriptions are too scanty to permit profitable tabulation. All the cases included for discussion have been reported in recent years since the introduction of modern methods of transfusion. No serious effort has been made to study systematically the literature prior to the recognition of blood groups. It is of interest to know that reactions with severe renal involvement occurred during the course of the earlier experimental work. Ponfik,³ in 1875, gave a full description of reactions of this kind in dogs given transfusions of foreign blood. Lévy⁴ (1904), in an investigation of the renal changes found in experimental hemoglobinuria, cited a number of earlier contributions to the study of this subject. Lindau⁵ (1928) presented a large bibliography which covered many of the more recent studies.

REPORT OF CASES

CASE 1—A white woman, a housewife, aged 46, was admitted to the medical service of Johns Hopkins Hospital on April 1, 1929, complaining of weakness, loss of weight and insomnia. She had had pneumonia in childhood but no other serious illness. There was no suggestion of previous nephritis or disease of the urinary tract. She had been married at 23 years of age, and had five healthy children, the youngest being 7 years of age. Following the birth of the last child, there had been a definite change in menstruation, the flow becoming more profuse and lasting seven days. She began to "fail" about two years before admission, when her appetite became poor and she had insomnia. After that there had been increasing pallor, nervousness, palpitation and finally shortness of breath on exertion and edema of the ankles. The loss of weight had been 50 pounds (22.7 Kg) in two years, her weight dropping from 150 pounds (68 Kg) to 100 pounds (45.4 Kg).

Physical Examination—There was great emaciation, and profound pallor of the skin and mucous membranes. There was no jaundice or enlargement of the superficial lymph nodes. The patient had many carious teeth. The heart was a trifle enlarged to percussion, the apex impulse was readily visible, there was a loud systolic murmur of maximum intensity in the pulmonic area. The pulse was full, with a rate of 100 per minute. The blood pressure was 105 systolic, and 45 diastolic. The abdominal muscles were relaxed and atonic. The margin of the liver was palpable, the spleen was definitely enlarged, extending from 4 to 5 cm.

3 Ponfik. Experimentelle Beiträge zur Lehre von der Transfusion, Virchows Arch f path Anat **62** 273, 1875.

4 Levy, L. Untersuchungen über die Nierenveränderungen bei experimenteller Hamoglobininurie, Deutsches Arch f klin Med **81** 359, 1904.

5 Lindau, A. Reaktionen nach Bluttransfusion. Eine etiologische und pathologisch-anatomische Studie, Acta path et microbiol Scandinav **5** 382, 1928.

below the costal margin, with the edge rounded, smooth and firm. Both kidneys were readily palpable. The vaginal outlet was relaxed, there was a profuse, yellowish, foul-smelling leukorrhoea. The cervix was soft and patulous and the fundus of the uterus was slightly enlarged. Moderate pitting edema was found over both tibiae.

The urine, on admission, was acid, with a specific gravity of 1.012, analysis revealed albumin ++, many leukocytes and a few granular and hyaline casts but no red blood corpuscles. The blood test showed hemoglobin, 20 per cent, red blood cells, 1,800,000, white blood cells 5,000 with a normal differential count. In the smears the red corpuscles appeared pale, and there was marked poikilocytosis. There was 0.6 per cent reticulocytes and the platelet count was 332,500. The bleeding and clotting times were normal. The fragility of the erythrocytes was within normal limits. The Wassermann reaction of the blood was negative. The van den Bergh reaction was indirect showing 0.2 mg of bilirubin per hundred cubic centimeters. The nonprotein nitrogen content was 20 mg per hundred cubic centimeters, the uric acid, 2.7 mg, and the blood sugar, 87 mg. The phthalein excretion was 65 per cent in two hours. Gastric analysis showed no free hydrochloric acid after stimulation with histamine. Roentgenologic studies of the chest and the entire gastro-intestinal tract revealed nothing of importance.

It was decided that the anemia was probably due to loss of blood from the uterus, and in order to prepare the patient for a uterine curettage and a possible laparotomy, blood transfusion seemed the procedure of choice. Previous to the transfusion the albuminuria had subsided to a bare trace and the casts had disappeared.

The patient and the selected donor were both reported by the laboratory to be members of group II (Moss). Direct matching of the blood showed no cross-agglutination after two hours. After the transfusion this work was all rechecked and it was found that after standing two hours the cells of the donor showed slight agglutination in the recipient's serum. Regrouping revealed the fact that whereas the donor was of group II, the recipient was of group IV (Moss). Fresh, citrated blood was used for the transfusion, which was begun early in the afternoon of April 5. The events that accompanied the injection of blood are of such interest that they will be related in detail.

Transfusion and Immediate Reaction—The injection, which was controlled by a 20 cc syringe, proceeded slowly. During the introduction of the first 20 cc there was an abrupt fall in pulse rate from 90 to 70 per minute, and the patient complained of "creepy sensations" all over her body. She said that her head felt full and tight "as though it were going to burst." The subjective change seemed so definite that five minutes was allowed to pass before the injection was continued. A second 20 cc was introduced cautiously. The pulse rate, which had risen to 90, again fell to 70 and the patient complained of a severe headache. Her face became suffused, there was fullness of the veins of the neck, respiration grew shallow and labored, she became nauseated and soon vomited. The blood pressure at this stage was 120 systolic and 60 diastolic, just where it had been the previous day. It was decided to discontinue the transfusion and the needle was removed from the vein. After an interval of twenty minutes, the patient announced that she was feeling fine. We were so confident of our blood matching that the transfusion was resumed. It took five minutes to inject the third 20 cc and during this period, although the pulse fell from 90 to 60, there were no untoward symptoms, and the blood pressure remained at 120 systolic and 60

diastolic After a pause of five minutes, the fourth 20 cc was injected and again the pulse fell from 90 to 70 In five minutes the pulse had returned to 90 There were no symptoms as the fifth injection of 20 cc was started Scarcely 10 cc had been injected when the patient suddenly complained of lumbar backache, fulness of the head, nausea and faintness She became short of breath and cyanotic, the pulse rate rose rapidly and the beats could barely be detected at the wrist The transfusion was discontinued at 4 30 p m, after a total of 90 cc had been injected

At 4 45 p m there was a violent chill and the patient had an involuntary stool The temperature was 101.8 F, the pulse rate 128 and the respiratory rate 26 At 5 15 p m the chill ended, but cyanosis was still marked and respiration was rapid and deep There was considerable spontaneous bleeding from the venipuncture wounds in both arms, which could be controlled only by the application of pressure bandages At 5 30 p m, the temperature was 104.6 F, the pulse rate 142 and the respiration rate 38 At 6 00 p m, she said that she felt warm and sleepy, she was perspiring freely and the temperature was 106 F By 7 00 p m, the temperature had fallen to 104.6 F, the pulse rate to 118 and the respiration rate to 28, cyanosis had disappeared and she was breathing freely At this point moderate vaginal bleeding was first noted (menstruation was not due until seven days later) After a night's sleep, she felt fairly well At 5 00 a m April 6, she voided 100 cc of coffee-colored urine, containing much hemoglobin, albumin +++ a few red blood cells and no casts At 6 00 a m the temperature was 100.8 F, the pulse rate 98 and the respiration rate 22 At 8 00 a m, she again voided 100 cc of dark brown urine She complained of anorexia and nausea and vomited at noon At 5 00 p m, she passed 25 cc of dark urine In spite of the fact that the temperature had risen to 102 F she felt better in the evening and ate a good supper

Posttransfusion Course and Delayed Reaction—The course can best be followed in figure 1

On April 7, 8, and 9, the patient seemed to be recovering satisfactorily from what was thought to be a hemolytic "incompatible" transfusion reaction The hemoglobinuria, jaundice, and vomiting, which had been striking features on the day after transfusion, subsided rapidly and finally disappeared Transfusions of citrated group IV (Moss) blood on April 7 and 9 (550 and 500 cc, respectively) were followed by mild "citrate" reactions without additional symptoms Urinary suppression, which was marked on April 7 and 8, attracted little attention at the time On each of these two days there was only a single small voiding which unfortunately was not measured

In the afternoon of April 9 (the fourth day after transfusion), though she seemed to be improving in every respect, the patient displayed a peculiar apprehension She said that she had a "funny feeling" in her head and that there were films before her eyes She announced that she was going to die, and despite reassurance persisted in this opinion On April 10, apprehension and agitation became more marked, that night she carried on a lengthy, rambling conversation with a neighboring patient which she did not remember on the following morning She was continually talking of death On the night of April 11, she talked irrationally, and her husband told us that she seemed to him "entirely out of her head" On the morning of April 12, she decided that she did "not wish to die in the hospital" and insisted on being taken home Aside from these queer and unexplained mental reactions, the patient appeared to be doing well At 4 p m on April 12 (8 days after the transfusion), she suddenly had a generalized convulsion lasting 15 minutes and passed into a state of semicoma In the evening she became completely comatose and had frequent generalized convulsions

At 7 00 p m, large, bruise-like, purplish spots appeared on both arms and a small, fresh hemorrhage was seen in the fundus of the left eye. A few hours later, a fine petechial eruption was noted at the base of the neck. Studies of the blood at this point showed normal bleeding and clotting times, with normal retraction

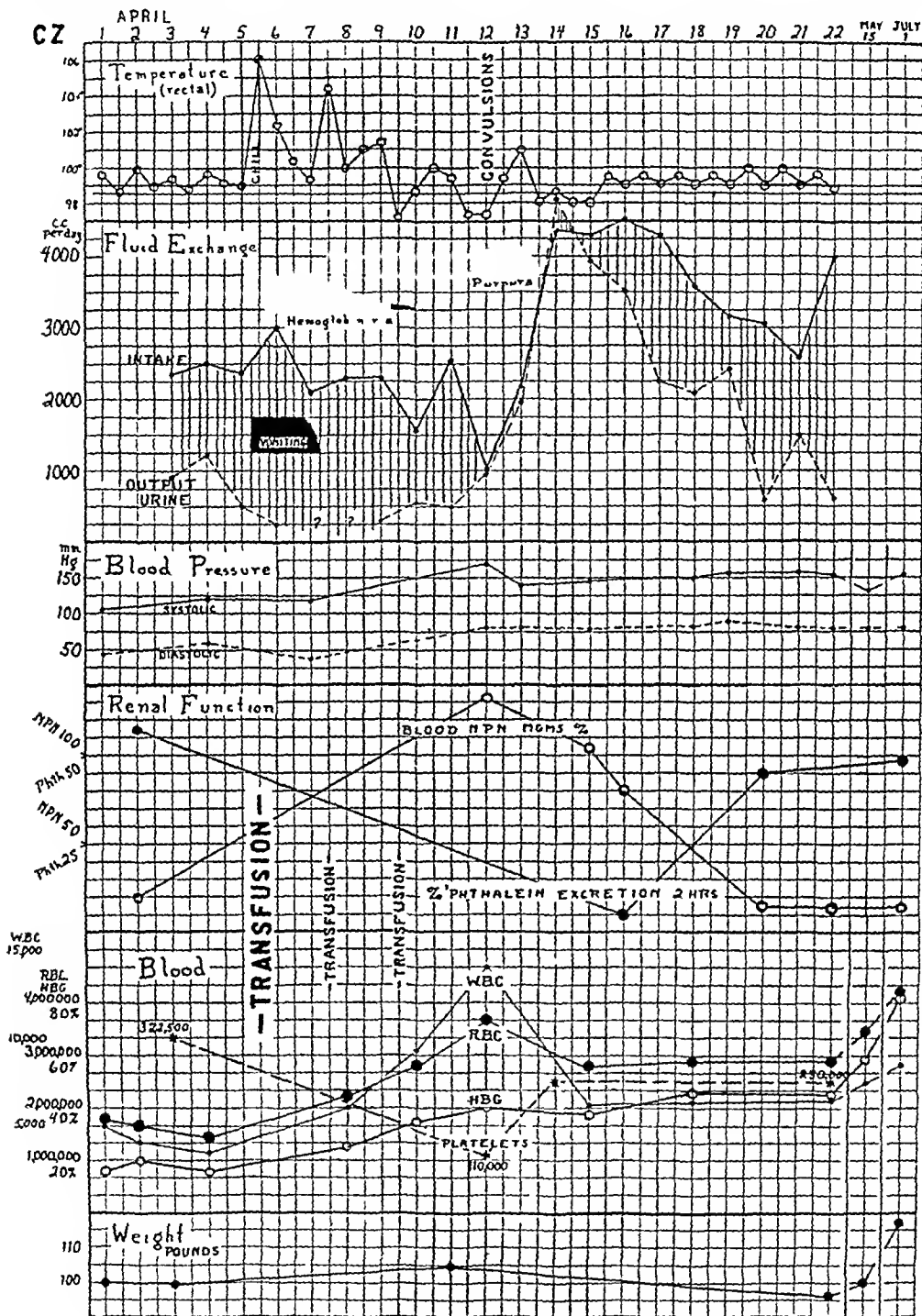


Fig 1 (case 1)—Course of a patient belonging to group IV (Moss) who received 90 cc of blood from a donor belonging to group II. There was an immediate reaction with chill, fever and vomiting, soon followed by hemoglobinuria and urinary suppression. Uremic manifestations, including convulsions and coma, appeared on the eighth day. Recovery was associated with diuresis.

of the clot. The platelet count, however, had fallen to 110,000. The van den Bergh reaction was negative. There had been a remarkable rise in blood non-protein nitrogen to 132 mg per hundred cubic centimeters.

Early in the morning on April 13, she regained consciousness. At 9 00 a m, she was oriented but drowsy and listless. The urine showed a trace of albumin and a few red blood corpuscles. Together with the symptomatic improvement on that day, the urinary suppression gave way to diuresis, which on the next day amounted to 5,000 cc of urine in twenty-four hours. As the diuresis progressed the patient cleared mentally and the blood nonprotein nitrogen content fell gradually to normal. The details of the clinical course are clearly indicated in figure 1.

Additional studies which do not appear in the chart are: On April 16, examination of blood showed uric acid, 5.4 mg per hundred cubic centimeters, creatinine, 2 mg, carbon dioxide combining power of plasma, 49.4 per cent by volume and phosphorus, 7.5 mg per hundred cubic centimeters. On April 23, the cerebrospinal fluid showed neither cytologic nor serologic abnormality.

By April 25, the patient had completely recovered from the effects of the delayed transfusion reaction.

Subsequent Course—On May 9, she seemed in excellent condition for operation and was sent to the gynecologic service where a dilation and curettage operation was performed, and a cervical polyp removed. The gynecologic diagnosis was hyperplasia of the endometrium, benign cervical polyp and chronic endocervicitis.

When discharged from the hospital on May 15, the patient's blood was well above its level on admission, the nonprotein nitrogen content had fallen below 30 mg per hundred cubic centimeters. The phthalein excretion had risen to 50 per cent in two hours, the urine was entirely normal and the blood pressure was 134 systolic and 80 diastolic.

After discharge she returned to the hospital frequently for follow-up examinations. When seen on July 1, she seemed perfectly well, had gained 20 pounds (9 Kg) in weight, and the blood picture, urine, phthalein excretion and nonprotein nitrogen of the blood were all entirely normal (fig 1).

Summary—A transfusion with 90 cc of incompatible blood was followed by an immediate reaction with shock, chill, fever, vomiting, hemoglobinuria, jaundice and urinary suppression. The acute symptoms subsided but the urinary suppression continued. A secondary, delayed reaction, which reached its peak on the eighth day after transfusion, was characterized by agitation, psychosis, hypertension, reduced phthalein excretion, nitrogen retention, purpura, convulsions and coma. Recovery began on the ninth day and was associated with considerable diuresis. Three months later the patient was well.

CASE 2—A white man, aged 52, had been sick for about three years, he was first admitted to the Johns Hopkins Hospital in July, 1922. The diagnosis was pernicious anemia. The blood examination showed red blood cells, 1,200,000, hemoglobin, 32 per cent, and white blood cells, 5,200. The urine was normal. The phthalein excretion was 57 per cent in two hours. The blood was found to be group IV (Moss). The patient was given five transfusions of blood from group IV. He was discharged much improved, showing red blood cells 4,000,000, hemoglobin 60 per cent and white blood cells 8,000. He was readmitted to the hospital on Jan 26, 1923 during a relapse. On January 28, he was prepared for transfusion. In the existing record there is no laboratory report of blood-grouping or cross-matching previous to this transfusion, though from the established practice in the hospital and the remarks in the record, one may presume that cross-matched group IV (Moss) blood was utilized. The important data following this transfusion are presented in figure 2.

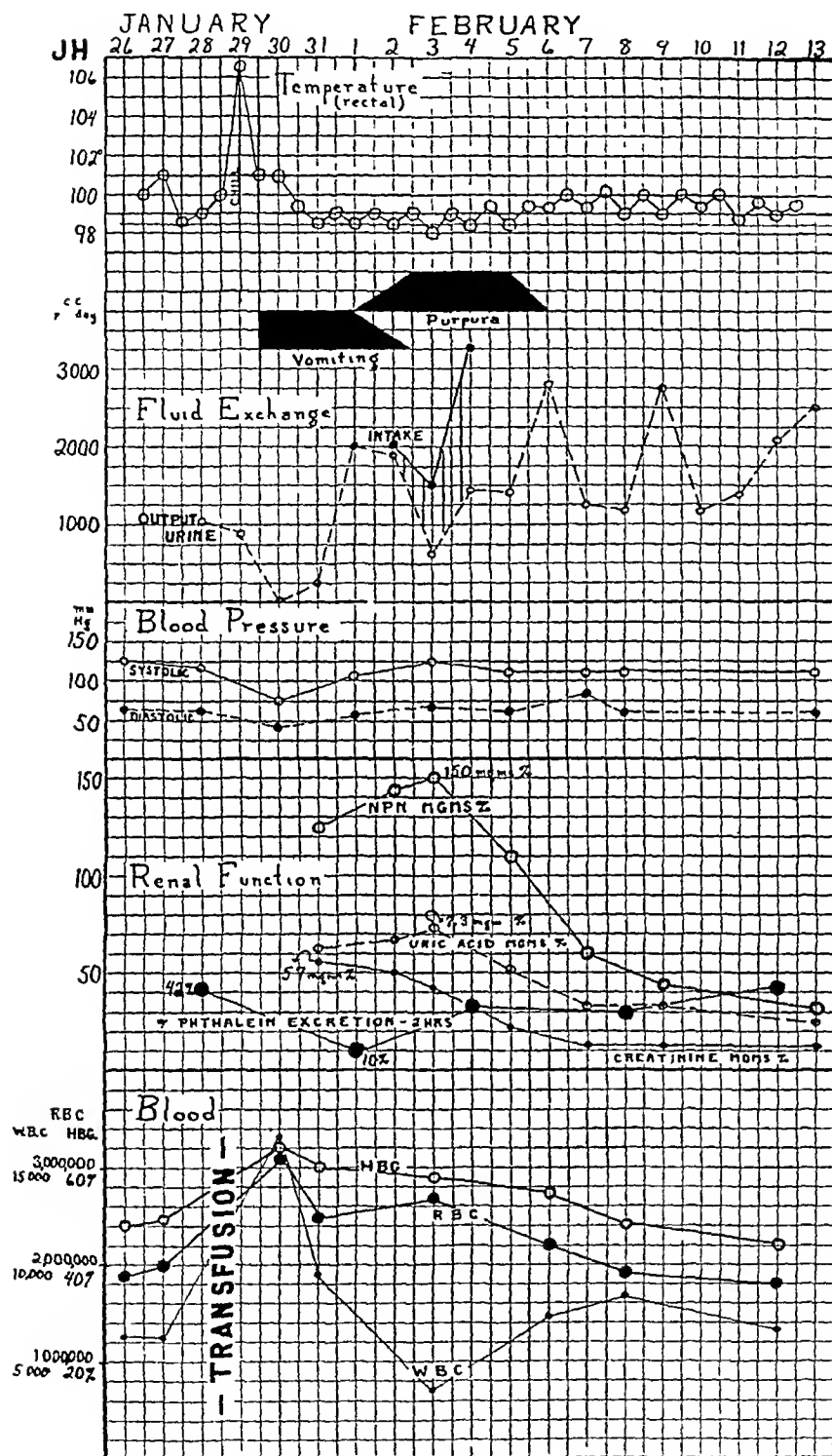


Fig 2 (case 2) —Course of the reaction of a patient who was given 500 cc of blood which was probably incompatible. Note the similarity between the chart of this patient and the chart in case 1.

As I did not see the patient, I quote the progress notes from the record

January 28 The patient received 500 cc of citrated blood, about thirty minutes later there was a slight chill. In one hour the temperature was 100.4 F, in two hours, 104 F and in three hours 106.7 F. There was considerable nausea and some vomiting. Morphine quieted him and in four hours the temperature was 104 F, but the heart sounds were weak, at times they were slow and at other times rapid. The blood pressure could not be determined and the patient was practically pulseless at the wrist.

January 31 The patient was more deeply jaundiced. He voided 275 cc of urine, the first since the transfusion (?). The urine contained red blood cells, casts, albumin and a great quantity of urobilin.

February 1 A fine hemorrhagic pruritic eruption appeared on the arms and legs.

February 2 The patient seemed better, his color was not so yellow. The rash was slightly elevated and did not fade on pressure. It was composed of pinpoint hemorrhagic spots.

February 3 The patient was weak and still nauseated, but severe vomiting had not been present since January 31. He had no appetite. The purpuric eruption was extensive and bright. It was almost confluent over the inner surface of the calves and the right forearm. The pectoral folds, the inner surface of the thighs, the buttocks and the inner aspect of the left elbow were thickly peppered with fine, bright petechiae. The abdomen and the chest were sparsely sprinkled with petechiae. The nose had been irritated and a thin blood-tinged fluid was occasionally blown out. There were no hemorrhages in the conjunctival or the buccal mucosa. The eyegrounds showed no hemorrhages.

February 5 The patient was much improved. The nausea had diminished. There was less jaundice and the rash was fading.

February 6 The purpuric eruption had disappeared.

The patient ultimately recovered from this reaction and returned home without another transfusion. On February 15, about two weeks after the transfusion, agglutination tests were made and it was noted that "the patient now shows group II (Moss) blood." It is of interest that there were two subsequent admissions to the hospital in 1923 and 1924. The blood was always found to belong to group II (Moss), but there was much difficulty in obtaining proper cross-matching with prospective donors. He was given five large transfusions with group II (Moss) blood, some followed by mild reactions and others without symptoms. He died during a violent immediate reaction on April 10, 1924, following the injection of 250 cc of group II cross-matched blood.

Summary—A transfusion with 500 cc of what was probably incompatible blood was followed by an immediate reaction with chill, fever, collapse, vomiting, jaundice, urinary suppression and urobilinuria. Following this, there was a delayed reaction which reached its peak on about the eighth day after the transfusion and which was characterized by purpura, nitrogen retention, reduced phthalein excretion and slight rise in blood pressure. Recovery was coincident with a rise in the phthalein excretion and a fall in the nonprotein nitrogen content of the blood.

CASE 3—A white man, aged 39, was first admitted to the Johns Hopkins Hospital in October, 1920, during the fourth relapse of a characteristic pernicious anemia. In the hospital the disease underwent spontaneous remission. He was discharged after the blood had improved from a red blood cell count of 1,648,000 with 42 per cent hemoglobin, to a red blood cell count of 3,768,000 with hemoglobin, 75 per cent. The urine was normal. The patient was readmitted on May

20, 1922, during the seventh relapse The blood showed red blood cells, 1,336,000, hemoglobin, 30 per cent, and white blood cells, 4,000 The blood was found to be group IV (Moss)

On May 29, utilizing blood which had been tested for cross-agglutination, a transfusion was attempted but was stopped immediately because "the patient became cyanotic, his face began to swell, his breath came with difficulty and he finally collapsed" On June 10 he was given a transfusion of 750 cc of citrated blood without an immediate or subsequent reaction On June 30, a third transfusion was undertaken with blood that had previously been tested for cross-agglutination The more important features of the course following transfusion are recorded in figure 3 As I did not see this patient, I quote the following remarks from the progress notes in the record

June 30 The patient was given a transfusion After 50 cc had been injected, the patient began to complain of a smothering sensation Atropine, 0.01 gram (0.00065 Gm), and epinephrine, 15 minims (0.92 cc), relieved this and the injection proceeded After 350 cc had been injected the patient vomited and had a chill and the injection was stopped The temperature rose to 104.5 F and the patient could retain nothing by mouth for eight hours

July 1 The urine was clear and straw colored, it contained no albumin The guaiac reaction was negative

July 2 The reaction from the transfusion had subsided, but the patient still complained of nausea

July 4 For forty-eight hours the patient had been unable to retain anything by mouth

July 6 The urine was acid, with a specific gravity of 1.020, albumin + and the guaiac reaction negative

July 7 The patient had vomited for three days Since the day before, his respirations had been deep and slow, hyperpnea was pronounced and the patient was drowsy

July 8 The urine was acid, containing albumin + + + +, and hyaline and granular casts The guaiac reaction was negative The blood showed nonprotein nitrogen, 186.3 mg per hundred cubic centimeters, and carbon dioxide combining power, 18.7 per cent by volume

July 10 The blood showed nonprotein nitrogen, 186 mg per hundred cubic centimeters, sugar, 123 mg, creatinine, 10.1 mg, chloride, 486 mg, and carbon dioxide combining power, 22.5 per cent by volume For twenty-four hours there had been marked oliguria, a state of semicoma and convulsions The patient could not be roused There were tracheal rales He had labored breathing The face had a curious suffused look No jaundice was apparent He gave some evidence of discomfort on pressure in the right upper abdominal quadrant Shortly after this note was made, the patient died

Autopsy—In addition to the changes in the liver and kidneys, which will be described in detail, the following points are of interest There was slight edema of the ankles, general pallor of the organs, well preserved subcutaneous fat which had a characteristic bright, lemon-yellow tint, bilateral hydrothorax (300 cc on each side) and a few small areas of fresh lobular pneumoma The spleen was enlarged (520 Gm) In microscopic preparations there was no striking abnormality of the spleen, the malpighian bodies and venous sinuses stood out sharply, many erythrocytes were in the sinuses and scattered through the reticulum, there were a few scattered myelocytes, mostly eosinophilic The bone-marrow was hyperplastic, containing many normoblasts and megaloblasts and a moderate number of megalokaryocytes

The liver was large (2,600 Gm), its surface was smooth and grayish red with indistinct lobulation. For microscopic study only hematoxylin and eosin preparations were used, the tissue was not available for other stains. The lobules were arranged normally and the parenchymal cells were cloudy, many small vacuoles were apparently due to deposits of fat. Nearly all of the cells, but particularly those of the periportal areas, were sprinkled with fine, yellowish-brown pigment.

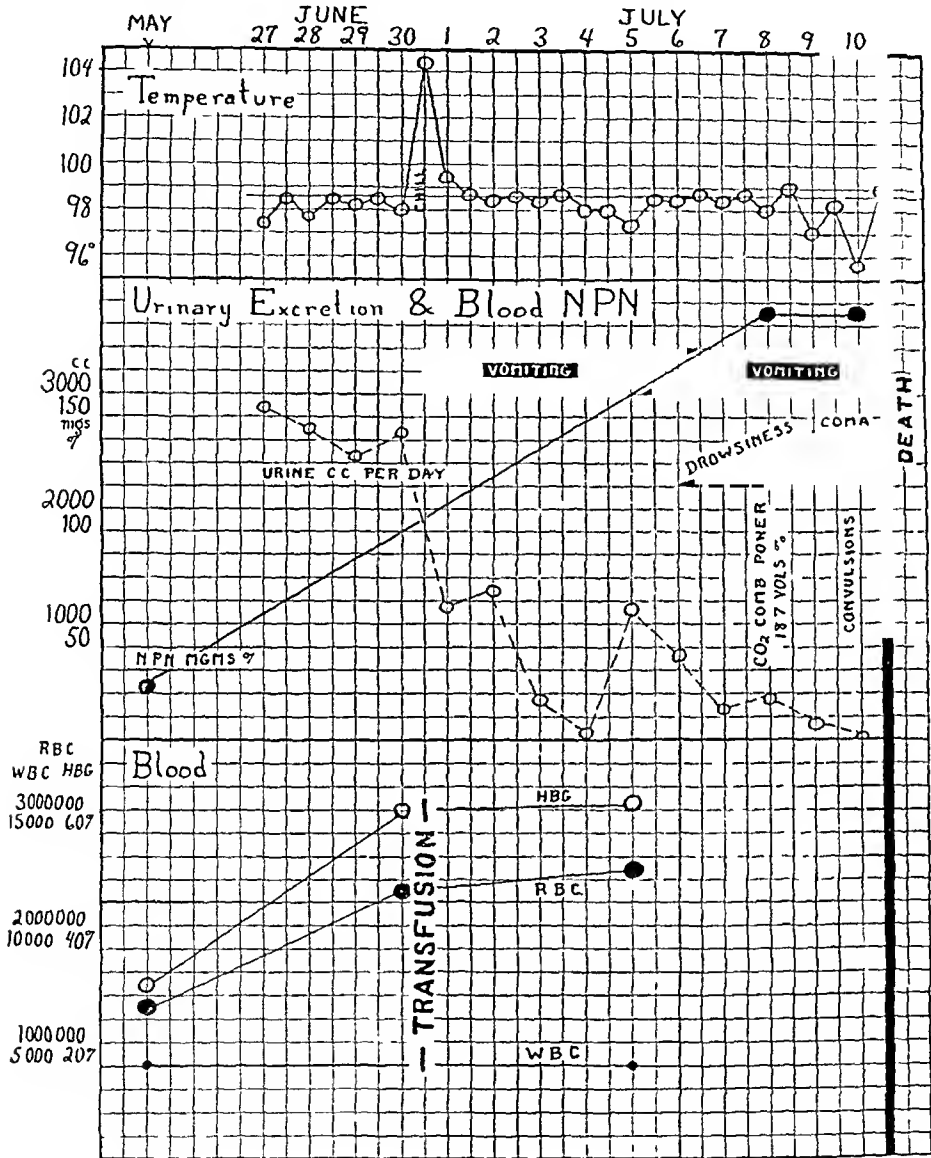


Fig 3 (case 3)—Course of a patient who was given a transfusion of 350 cc of blood. An immediate reaction was followed by persistent vomiting and oliguria. Uremic manifestations developed gradually and the patient died on the eleventh day.

granules. There was distinct central atrophy, and in addition a number of central necroses, in some of which the nuclei were no longer visible and the normal cellular structure had been replaced by smooth hyaline and fibrous tissue, in which there was a scattering of lymphocytes and a few large, pigment-laden mononuclear cells with shrunken nuclei.

The kidneys were large, the right one weighing 289 Gm and the left one, 300 Gm. The capsule stripped easily leaving a smooth, grayish-red, glistening surface. The cortex was 7 mm in thickness, dull, yellowish gray and rather translucent, the striae were fairly distinct. The glomeruli were readily visible as pale yellow, translucent elevated dots. The pyramids were of much deeper red color. Several small, dark red hemorrhages were present in the mucosa of the right renal pelvis. The ureters were patent. Microscopic examination showed the capsular surface to be regular. The tubules were widely separated by loosely arranged, edematous tissue, in which only a few delicate strands took up the pink of the van Gieson stain. There were a few inconspicuous, old fibrous scars containing clumps of lymphocytes. There was a remarkable cellular

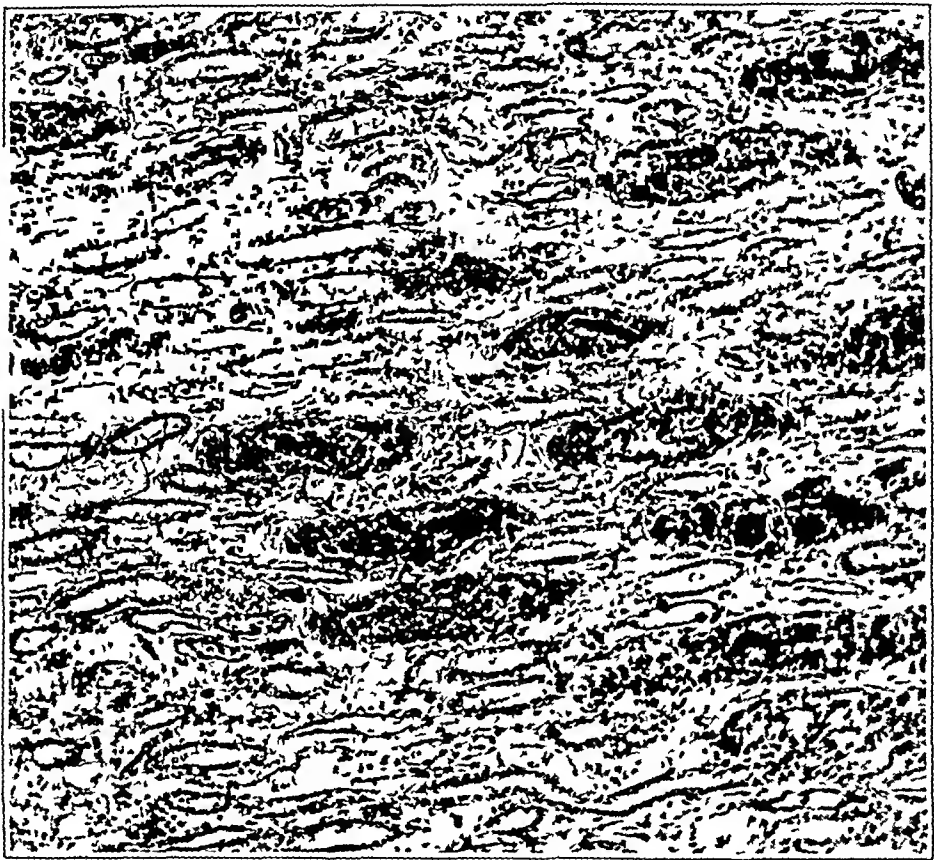


Fig 4 (case 3) —Photomicrograph of the kidney, showing a group of collecting tubules, many of them containing blood pigment, cells and debris, $\times 90$

infiltration throughout the edematous interstitial tissue, most of the cells were lymphocytes, but there were a number of small groups, some of them periarterial, in which there was a striking number of large, mononuclear wandering cells and polymorphonuclear leukocytes. The arteries and veins were not remarkable. The glomeruli appeared large, with a relatively wide intracapsular space. A few glomerular capsules showed slight fibrous thickening, but the capillary tufts were everywhere normal and there was no evidence of acute or progressive glomerular disease. After examining many sections it was possible to demonstrate two or three obliterated and fibrosed glomeruli. The tubules of the cortex had large lumina and flattened epithelial cells, in a few of which the cytoplasm was sprinkled with small grains and droplets of a brownish pigmented material. As one passed down the tubules toward the pelvis one found that the epithelial changes became more marked and that the cells grew larger and cloudier, they

were less firmly attached and contained more and larger droplets of brown pigment. In many of the collecting tubules the epithelial cells were packed with pigment droplets, they were frequently necrotic and in two or three places showed evidences of calcification. In some of the places where the necrotic epithelium had become detached, the tube was lined with a new layer of flat and apparently regenerating cells. The lumina of the cortical tubules contained nothing except occasionally a finely granular, pale, eosin-staining material and a few leukocytes. Following the tubules downward, one found their lumina filled with increasing amounts of debris, disintegrated leukocytes, desquamated epithelial cells and large phagocytic cells filled with yellowish-brown pigment. In addition to these there were, in increasing numbers, large and small globules of a conspicuous and peculiar material which requires more detailed consideration. In the

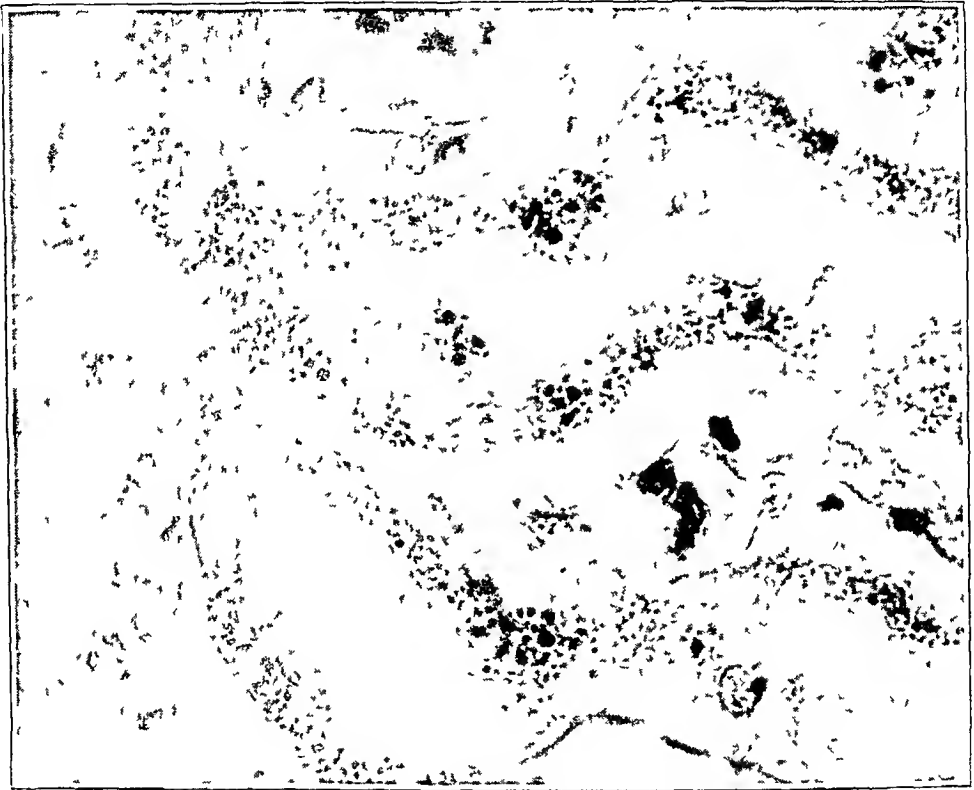


Fig 5 (case 3) —Photomicrograph of the kidney, showing two tubules, the epithelial cells of which contain the brownish, pigmented droplets described in the text. The section was stained lightly in order to make the droplets stand out as sharply as possible, $\times 580$

proximal levels of the tubules these peculiar droplets had almost the same staining characteristics as the erythrocytes of the adjacent capillaries, though they stained more deeply with eosin and less brilliantly with fuchsin. That they were not erythrocytes became apparent from a study of their contour and from their great variations in size. Passing further down the tubules one found that these droplets became less and less eosinophilic, and less and less fuchsinophilic. In the large collecting tubules they had in unstained preparations a rusty brown color. When stained with a fuchsin-methyl green technic (Altmann's aniline fuchsin and methyl green) they had a muddy, greenish-brown hue in which there was occasionally the faintest tinge of pink. The pigmented droplets within the epithelial cells, to which attention has been called, had similar staining

characteristics Various iron stains showed a few scattered granules in the epithelial cells which gave the characteristic iron color reactions (hemosiderin granules of pernicious anemia similar to those found in the liver), the peculiar pigmented droplets, on the other hand, both in the epithelial cells and within the lumina of the tubules, failed to take on the faintest trace of prussian blue

Summary—A patient with pernicious anemia was given a transfusion of 350 cc of blood that was thought to be compatible There was an immediate reaction with chill, fever, vomiting and suppression of urine The acute symptoms subsided, but vomiting and oliguria continued On the seventh day after transfusion, uremic manifestations were evident On the eleventh day, nitrogen retention, acidosis and marked albuminuria were observed, and the patient died in a state of coma At autopsy, the liver was large, contained considerable fat and fresh and healed central necroses The kidneys were swollen, edematous and infiltrated with leukocytes The renal epithelial cells showed a peculiar type of degenerative change in which the intracellular deposition of pigmented droplets was a conspicuous feature Many of the epithelial cells were necrotic and there was a suggestion of epithelial regeneration The tubules, especially the collecting tubules, contained large amounts of a similar pigmented material and in addition desquamated epithelial cells, leukocytes and granular debris

CASE 4 (Goormaghtigh⁶)—A man, aged 23, was given a transfusion four hours after being shot through the left axillary vein The immediate response was excellent, but oliguria followed On the third day, after an apparently normal course, agitation and vomiting set in Death occurred on the sixth day with anuria and a manifest hypertension

At autopsy, the liver showed degenerative changes in the central portion of the lobules The kidneys were large and microscopic changes were confined to the tubules, the proximal convoluted tubules were dilated with a flattening of the epithelium, there was desquamation of the epithelium of the distal convoluted tubules, the collecting tubules were packed with debris

CASE 5 (Bancroft⁷)—A woman, aged 49, had an incomplete abortion with hemorrhage and secondary anemia During transfusion she complained of pain in the lumbar region Immediately after the transfusion, a chill and fever were followed by urinary suppression The oliguria continued and vomiting was persistent The blood urea rose and the patient became edematous and irrational On the eighth day there were "spastic contractions" of both hands resembling tetany On the ninth day, the condition seemed desperate, and decapsulation of both kidneys was performed Following the operation there was marked diuresis with gradual recovery At operation the kidneys appeared "almost necrotic," they were large, gravish and friable

CASE 6 (Oliensis⁸)—A woman, aged 23, had chronic sinusitis, epistaxis, and secondary anemia Transfusion was followed by a severe immediate reaction, with shock, a chill, fever and vomiting, soon jaundice developed with urinary suppression Following this there was continued oliguria and vomiting, nitrogen retention, anasarca, stupor, dimness of vision and delirium Improvement was associated with diuresis that began on about the twelfth day Recovery was gradual

6 Goormaghtigh, N Note sur un cas de blocage du rein consécutif à la transfusion du sang, *Arch méd belges* **72** 611 (Dec) 1918

7 Bancroft, F W Anuria following Transfusion Effect of Decapsulation of Both Kidneys, *Ann Surg* **81** 733 (April) 1925

8 Oliensis, A E Acute Nephritis following Transfusion *M J & Rec* **128** 178 (Aug 15) 1928

CASE 7 (Shera⁹)—A woman, aged 36, had a ruptured ectopic pregnancy. Following transfusion there was a mild immediate reaction with a slight fever. On the second day, hemoglobinuria and jaundice developed with urinary suppression. The oliguria continued, but for several days the general condition seemed good. Nitrogen retention was noted on the fourth day, and on the seventh day, signs of uremia appeared. A period of drowsiness and irritability was followed by sudden death on the ninth day.

At autopsy, the liver was found to be of the "nutmeg" type with "parenchymatous degeneration." The spleen was engorged. The kidneys were large and pale, the tubules were filled with red blood cells and debris and the tubular epithelium was flattened.

CASE 8 (Lemke¹⁰)—A woman, aged 32, had a ruptured ectopic pregnancy. There was general improvement immediately after the transfusion but soon fever set in. From the day of the transfusion there was persistent vomiting, urinary suppression and epistaxis. The patient grew progressively worse, exhibited signs of uremia and died six days after the transfusion.

At autopsy, punctiform hemorrhages were found in the pleura and mucous membrane of the bladder. The liver showed numerous necroses located for the most part in the central portion of the lobules. The kidneys were pale, occasional glomeruli seemed swollen, the tubules were filled with cellular debris and finely granular or amorphous material giving the color reactions of hemoglobin, many collecting tubules were plugged with this material. The capillaries of the medulla were distended with blood, accumulations of small round cells were observed here and there between the tubules.

CASE 9 (Santy¹¹)—A woman, aged 30, had a ruptured ectopic pregnancy. The immediate results of a transfusion seemed favorable, but on the second day urinary suppression and hemoglobinuria were noted. The oliguria persisted and on the eighth day, following the development of pulmonary edema, the patient died. There was anuria during the forty-eight hours before her death.

CASE 10 (Boïdin, Berthaux and Beyrand¹²)—A young woman had prolonged typhoid fever with progressive anemia. There was a violent immediate reaction following transfusion, with a chill, collapse, fever and vomiting, followed by urinary suppression and "red urine." The oliguria continued and vomiting increased on the fifth day. On the sixth day, following generalized convulsions the patient became comatose, the coma lasted for four days. As consciousness was regained there was diuresis. The patient gradually returned to normal.

CASE 11 (Baker and Dodds¹³)—A woman, aged 38, had a gastric ulcer. She was given a transfusion during the operative anesthesia. An immediate

9 Shera, G. Fatal Suppression of Urine Caused by Latent Haemagglutinins, *Brit M J* **1** 754 (May 5) 1928.

10 Lemke, R. Pathologisch-anatomische Befunde bei Todesfällen nach Bluttransfusionen, *Virchows Arch f path Anat* **257** 415, 1925.

11 Santy, M. P. Nephrite aigue mortelle consecutive a une transfusion, *Lyon chir* **23** 608, 1926.

12 Boïdin, Berthaux and Beyrand. Petite transfusion de 40 centimètres cubes de sang citrate dans un cas de septicémie post-typhoïdique. Choc dramatique et accidents tardifs extrêmement graves, *Bull et mem Soc méd d hôp de Paris* **43** 869, 1919.

13 Baker, S. L., and Dodds, E. C. Obstruction of the Renal Tubules during the Excretion of Haemoglobin, *Brit J Exper Path* **6** 247 (Oct) 1925.

reaction was not noted, but the temperature rose after the operation. Following the development of hemoglobinuria, jaundice and urinary suppression, the patient's condition grew rapidly worse, coma set in and she died on the fourth day with marked nitrogen retention.

At autopsy the kidneys were pale, there was marked dilatation of Bowman's capsules and convoluted tubules with flattening of the epithelium of the latter. Small masses and granules of eosin-staining material were arranged loosely in the convoluted tubules but were tightly packed in the collecting tubules.

CASE 12 (Baker and Dodds¹³)—A woman, aged 54, had jaundice and cholelithiasis. There was an immediate transfusion reaction with collapse and fever followed by hemoglobinuria, urinary suppression, increasing nitrogen retention, coma and death on the eighteenth day.

At autopsy, nodular cirrhosis of the liver was noted. A large stone was found in the common bile duct. The kidneys were dark brown, the glomeruli and the convoluted tubules were normal, the collecting tubules were filled with polymorphonuclear and mononuclear cells and much eosin-staining, granular debris.

CASE 13 (Curtis¹⁴)—A young woman had myoma uteri with hemorrhage and secondary anemia. There was an immediate transfusion reaction with pain in the back and chill, followed by hematuria, urinary suppression and nitrogen retention. When last observed, two weeks after the transfusion, the patient was gradually recovering.

CASE 14 (Copher¹⁵)—The age and sex of this patient were not stated. Secondary hemorrhage developed following a nasal operation. There was no immediate transfusion reaction, but shortly afterward persistent vomiting began and there was suppression of the urine. On the second day, hemoglobinuria developed, followed by jaundice and enlargement of the liver. Hemorrhagic retinitis developed and the patient died eleven days after the transfusion.

CASE 15 (Witts¹⁶)—A woman, aged 29, had secondary anemia following pregnancy. During the transfusion she complained only of a headache. A few hours later there was vomiting and elevation in temperature. There was complete suppression of the urine until the sixth day, when the blood urea was 333 mg per hundred cubic centimeters. Throughout this period "her color and appearance were good and her mentality clear." On the ninth day, hypertension and tetany developed. On the tenth day, the output of urine increased somewhat and the "condition of the patient seemed fair." At this time the blood urea was 354 mg per hundred cubic centimeters and the plasma bicarbonate was 33.6 per cent by volume. Death came suddenly on the eleventh day.

At autopsy, anasarca with bilateral hydrothorax and ascites was discovered. The kidneys were swollen and pale and showed a few petechiae. The glomeruli were large and anemic. The convoluted tubules contained albuminous material. The junctional tubules contained deeply eosinophilic granules or small spheres. "Numerous collecting and junctional tubules" and "most of the discharging tubules" were filled with granules, lumps and masses of an "isotropic substance of the color of brown sugar", in addition there were leukocytes and

14 Curtis, A. H. Anuria following Blood Transfusion, *Surg. Gynec. Obst.* 30: 627, 1920.

15 Copher, G. H. Blood Transfusion. A Study of Two Hundred and Forty-five Cases, *Arch. Surg.* 7: 125 (July) 1923.

16 Witts, L. J. Note on Blood Transfusion with an Account of a Fatal Reaction. *Lancet* 1: 1297 (June 22) 1929.

desquamated epithelial cells. The cytoplasm of the desquamated cells was "finely granular and of the same color as the granules and lumps." The interstitial tissue was edematous and infiltrated with round cells. The change in the kidneys was spoken of as "hemoglobin infarction." The liver was not described.

CASE 16 (Lindau⁵)—A man, aged 35, had a history of duodenal ulcer. He was given a transfusion because of a gastric hemorrhage following resection of the stomach. It was thought from the agglutination tests before the transfusion that the donor and the recipient both belonged to group IV (Moss). Subsequent to the transfusion, careful studies of the blood were carried out by Forssman and Fogelgren¹⁷. It was found that the recipient belonged to group IV (Moss) and the donor to group II (Moss). After 75 cc of blood had been injected, the patient became pale and pulseless and lost consciousness. Because of this reaction the transfusion was stopped temporarily, but was soon resumed and a total of 450 cc of blood injected. One hour later, there was a chill followed by fever and hemoglobinuria. During the next three days only from 20 to 50 cc of urine was passed. The blood nonprotein nitrogen increased gradually and on the day of the patient's death it reached 234 mg per hundred cubic centimeters. Death occurred during uremia on the sixth day after the transfusion.

At autopsy, there was no icterus, cutaneous hemorrhage or edema. The liver was of normal size, there was no gross abnormality, microscopically, a number of central and irregularly arranged necroses were found. The kidneys were slightly enlarged. There was the "nephrotic type" of degenerative changes in the epithelial cells of the renal tubules. There were masses of hemoglobin in the lumina of the collecting tubules, these were rose colored in the proximal levels and yellowish brown in the distal levels. The interstitial cellular infiltration of the kidneys was of such a character as to suggest foci of blood formation. A large ulcerated area was seen in the sigmoid portion of the colon. There were hemorrhages in the mucosa of the urinary bladder. Sero-sanguineous fluid was observed in the pleural and the peritoneal cavities.

CASE 17 (Lindau⁵)—A woman, aged 28, had cholecystitis. There was hematemesis following cholecystectomy. The patient was somewhat restless during the early part of the transfusion but she soon became quiet. One hour after the transfusion, a chill was followed by fever and hemoglobinuria. From this point on, there was oliguria. On the sixth day, the blood nonprotein nitrogen reached 150 mg per hundred cubic centimeters. The patient became stuporous, vomited a great deal and finally died in uremia on the tenth day.

At autopsy, there was a bilateral bronchopneumonia. The kidneys were somewhat swollen, and in microscopic studies they showed essentially the same changes described in case 16. The degeneration of the epithelial cells of the renal tubules was more advanced, there was epithelial desquamation and regeneration. The liver was not studied.¹⁸

17 Forssman, J, and Fogelgren, G. Ein Todesfall nach Bluttransfusion von Person zu Person mit "gleicher" Blutgruppe, *Klin Wchnschr* 6 1663 (Aug 27) 1927.

18 Lindau's case 3 (footnote 5) has not been included in this series. The patient was an old man very ill with hypernephroma, who died thirty-six hours after the transfusion. The clinical data are incomplete, but the autopsy observations are of great interest. The tubular epithelial cells of the kidneys showed early degenerative changes. Hemoglobin was found in the lumina of the loops of Henle, but practically none was present in the collecting tubules. The liver showed fresh foci of necrosis.

Additional Cases—In addition to the foregoing cases, which have been summarized in table 1, brief mention should be made of several other reported cases in which the posttransfusion course was of the same character. Hirsch,¹⁹ in a discussion of blood transfusion, mentioned a young woman who was given blood without previous grouping or cross-agglutination tests. Soon after the transfusion there was a chill, then jaundice and oliguria, and finally uremia, with death on the ninth day. Pribram²⁰ observed the same type of reaction, with oliguria and an extreme grade of nitrogen retention. Death occurred three or four days after the transfusion, at autopsy, masses of hemoglobin were found in the tubuli recti of the kidneys, completely occluding some of them. Enderlein²¹ observed a person in whom transfusion was followed by anuria which continued until the patient's death three days later.

In a series of 4,000 transfusions Brines²² had three cases in which this same peculiar reaction occurred. "The reactions were typical, consisting of a chill, an elevation in temperature, lumbar and abdominal pain, some dyspnoea and either oliguria or anuria. The blood urea became elevated, symptoms of uraemia were apparent, coma followed, and death intervened in from four to eight days." Brines said that "in all of these patients a previously well established diagnosis of chronic nephritis had been made." He mentioned no autopsy observations, and one is led to wonder just how much the chronic nephritis had to do with this "typical" reaction.

Lemke,¹⁰ in addition to the case cited (case 8), reported one in which the patient showed a delayed reaction of a slightly different type. A transfusion with 1,000 cc of blood that may have been incompatible was followed by a chill and fever. The temperature did not fall to normal, the patient became restless, then stuporous, and died on the tenth day. Throughout this time the urine was normal, and contained no trace of hemoglobin (the quantity of urinary excretion was not specifically mentioned). At autopsy, there were numerous hemorrhages throughout the mucous and serous surfaces. The liver showed necroses similar to those described in Lemke's first case (case 8). Aside from arteriosclerosis, the kidneys showed nothing of significance.

Butka²³ and Herrmann²⁴ reported cases in which delayed transfusion reactions were characterized by purpura with extensive hemorrhagic eruptions and bleeding from the mucous surfaces. One patient died six days, and the other three weeks, after the injection of the blood. In neither of these cases was urinary suppression specifically mentioned.

Grossmann²⁵ recorded the case of a woman, 24 years of age, who had a large intra-abdominal hemorrhage as the result of a ruptured fallopian tube. She was given a transfusion of 500 cc of the bloody fluid obtained from the abdominal cavity. Shortly after the transfusion, hemoglobinuria was noted. This was followed by persistent oliguria and the patient died in uremic coma six days later.

19 Hirsch, M. *Wien med Wchnschr* **74** 1722, 1924.

20 Pribram, E. *Arch f klin Chir* **133** 77, 1924.

21 Enderlein, quoted by Lemke (footnote 10).

22 Brines, O. A. *Fatal Post-Transfusion Reactions*, *J A M A* **94** 1114 (April 12) 1930.

23 Butka, H. E. *Transfusion with Universal Donor—A Fatality*, *California & West Med* **24** 74 (Jan.) 1926.

24 Herrmann, H. *Hämorrhagische Diathese nach Bluttransfusion*, *Med Klin* **19** 722 (May 27) 1923.

25 Grossmann, H. *Eigenbluttransfusion mit tödlichem Ausgang*, *Zentralbl f Gynak* **48** 2065 (Sept 20) 1924.

Summary of Clinical Data

Case	Age	Sex	Diagnosis	Transfusion Data			Immediate Reaction			Interval Phenomena			Delayed Phenomena					Result	Comment			
				Blood Group (Moss)	Recipient	Donor	Cross agglutination	Method	Amount, Cc	Chill	Fever	Urinary Suppression	Hemoglobinuria	Oliguria	Jaundice	Vomiting	Purpura			Nitrogen Retention	Central Nervous System Symptoms	Additional
1	46	F	Menorrhagia, secondary anemia	IV	II	IV	+	Citrate	90	+	+	+	+	+	+	+	+	Delirium, convulsions, coma	Fall in phthalein excretion, hypotension	8th day	Recovery	
2	52	M	Perineous anemia	?	II	IV	+	Citrate	500	+	+	+	0	+	+	+	+	0	Fall in phthalein excretion, edema	8th day	Recovery	Sixth transfusion
3	59	M	Perineous anemia	IV	?	IV	0	Citrate	750	+	+	+	0	+	0	+	+	Convulsions, coma	Acidosis	11th day	Death, autopsy	Third transfusion, second transfusion reaction
4	23	M	Hemorrhage, gun shot wound	?	?	?	?	Whole blood	520	0	+	+	0	+	?	+	?	Agitation, syncope	Hypertension	6th day	Death, autopsy	
5	49	F	Uterine hemorrhage, secondary anemia	?	?	?	0	Whole blood	400	+	+	+	0	+	0	+	+	Delirium, "tetany"	Edema	9th day	Recovery	Improvement followed decapsulation of kidneys
6	23	F	Epididymitis, secondary anemia	?	?	?	0	Whole blood	540	+	+	+	?	+	+	+	+	Vertigo, psychosis	Marked anasarca	12th day	Recovery	
7	36	F	Ruptured ectopic pregnancy	IV	IV	(same group)	+	?	500	0	+	+	+	+	?	?	+	Drowsiness, irritability		9th day	Death, autopsy	Transfusion during general anesthesia
8	32	F	Ruptured ectopic pregnancy	II	II	?	?	Whole blood	1,000	0	+	+	+	+	?	+	?	?	Eclampsia	6th day	Death, autopsy	
9	30	F	Ruptured ectopic pregnancy	?	?	?	?	Whole blood	170	0	+	+	+	+	?	?	?	?	Pulmonary edema	8th day	Death	
10	?	F	Typhoid fever, anemia	?	?	?	0	?	40	+	+	+	?	+	?	+	?	Convulsions, coma		12th day	Recovery	
11	38	F	Gastric ulcer	?	?	?	+	?	750	0	+	+	+	+	+	?	?	?		4th day	Death, autopsy	Transfusion during general anesthesia
12	51	F	Cholelithiasis	IV	IV	+	+	?	600	?	+	+	+	+	?	?	+	Drowsiness, coma		18th day	Death, autopsy	
13	?	F	Uterine hemorrhage	?	?	?	0	Citrate	?	+	+	+	+	+	?	?	+	?	Hemorrhagic icterus	? day	Recovery	
14	?	?	Nasal hemorrhage	IV	IV	+	+	Whole blood	620	0	0	+	+	+	+	+	?	?	Anasarca, hypotension, acidosis	11th day	Death, autopsy	
15	29	F	Secondary anemia	II	II	0	0	Citrate	?	0	+	+	0	+	0	+	+	"Tetany"		11th day	Death, autopsy	
16	35	M	Duodenal ulcer	IV	II	+	+	Citrate	450	+	+	+	+	+	?	?	+	?		6th day	Death, autopsy	
17	28	F	Cholecystectomy, hemorrhage	?	?	0?	?	Citrate	400	+	+	+	+	+	?	+	+	Stupor		10th day	Death, autopsy	

SUMMARY OF CLINICAL DATA

The Patient—The series is made up of seventeen patients, most of them relatively young adults. Anemia of some kind was present in all of them, but the cause of the anemia, its severity and the general condition of the patient at the time of transfusion seem to have had little influence on the occurrence of a reaction or its ultimate outcome. Reactions occurred so frequently in young persons who had been well until the onset of a sudden and severe hemorrhage that it would seem reasonable to exclude chronic illnesses, such as nephritis, heart disease, etc., from an important rôle in the causation of the response.

The Donor—In not a single case is there complete and satisfying evidence to prove that the blood of the donor was compatible with that of the recipient. Definite incompatibility was established in six cases. In two others (cases 4 and 9) there was probable incompatibility since transfusion was performed as an emergency measure without previous tests. The patient in case 2 seems to have presented an example of a queer change in blood group and was probably given incompatible blood. In case 8, cross-agglutination was not tested. In cases 3, 5, 10, 13 and 17, the statement is made that there was no cross-agglutination, but in none of these was the blood group of the donor determined, in only one was the recipient's group known. In case 6, the recipient and donor were of the same blood group (group not stated) and there was no cross-agglutination. In case 15, the recipient and donor were both of group II and there was no cross-agglutination. In none of the seven cases in which cross-agglutination was found satisfactory was there a retest of the agglutination reactions after transfusion, and the latter step, according to our experience in case 1 and Lindau's experience in case 16, would seem to be of considerable importance.

The Transfusion—The methods used in preparing and injecting the blood seem to have been of little importance, citrate was used in about half of the cases. On the other hand, the amount of blood injected was a significant factor in determining the final outcome. A definite statement of the amount transfused was made in fifteen of the seventeen cases, ten of these patients died and five recovered. In the five who recovered, the average amount injected was 314 cc, whereas the ten who died received an average amount of 564 cc. No patient receiving less than 350 cc died, and no one receiving more than 540 cc recovered. The patient who survived after a transfusion of 540 cc ran the most severe course of the recovered patients and until the twelfth day seemed on the verge of death.

Immediate Reaction—A severe immediate transfusion reaction occurred in all but seven of the cases. Two of these seven were under anesthesia during the injection of the blood and in them it is difficult

to attach much importance to the absence of this reaction. In at least six of the ten cases in which immediate reactions occurred, symptoms were first noted during the injection of blood, and in three of these the symptoms were of such severity that the injection was cut short. Detailed description of a fairly typical immediate reaction is presented in the history in case 1. The manifestations vary somewhat from case to case, but as a rule the characteristic features are a sense of great discomfort, signs of collapse, vomiting, chill and a sharp rise in temperature. The more acute symptoms rarely last more than a few hours, and as they subside hemoglobinuria is generally noted, it was observed in ten of the fifteen cases in which it was specifically looked for and it is possible that it was present in an eleventh instance in which the urine was described as "red." The first urine voided after the transfusion practically always contained albumin. Dating from the immediate reaction, there was suppression of urine in every one of the seventeen cases.

The Interval—In all instances, with the subsidence of the immediate reaction the patients seemed to improve. This interval of improvement lasted from a day or two to about a week, during which the patients were brighter and appeared to have derived distinct benefit from the transfusion. In six cases there was jaundice of a mild grade which disappeared after a day or so. There was no tendency for the hemoglobin and red blood corpuscles to decline, generally they showed an elevation over the pretransfusion level. Leukocytosis was noted in several cases. During the interval of improvement, the outstanding untoward feature was continued oliguria which, in a number of cases, was associated with persistent nausea and vomiting.

The Delayed Reaction—This was generally ushered in by symptoms of the central nervous system, of which agitation or drowsiness were the commonest. The symptoms began from a day or two to a week after the transfusion and progressed to a peak which was reached from the eighth to the twelfth day in the patients who recovered and from the fourth to the eighteenth day in the fatal cases. The outstanding observations were those usually associated with severe impairment of renal function, and belong to the syndrome commonly called uremia. In all cases in which the chemistry of the blood was studied there was considerable retention of nonprotein nitrogen and in one case, the carbon dioxide combining power of the plasma fell to 18.7 per cent by volume. The phthalein excretion in the two cases in which it was studied was markedly reduced. Edema was noted in five cases and was extreme in case 6. The blood pressure was definitely increased in cases 1, 4 and 15, but in several other cases in which it was followed there was no significant rise. Convulsions were observed in four cases and coma was noted in five cases. It is interesting that two of the five patients who became comatose

recovered. In three cases, there were definite purpuric phenomena at the peak of the reaction, and in a fourth case, frequent epistaxes were noted. In case 1, the purpura was associated with a fall in the platelet count.

The Outcome—Six patients recovered and eleven died. In the patients who recovered, the peak of the reaction was reached from the eighth to twelfth day. In the fatal cases death occurred between the fourth and eighteenth day, with ten days as the average duration of life after transfusion. All eleven deaths occurred with uremic manifestations. Recovery was associated with considerable diuresis beginning at the peak of the reaction. Only in case 5 did recovery seem to result from any radical form of treatment, in this instance, decapsulation of the kidneys was performed. In several other cases, spontaneous recovery was as dramatic as the result in case 5. We cannot be sure that the decapsulation of the kidneys was responsible for the happy outcome.

SUMMARY OF AUTOPSY MATERIAL

Though nine of the seventeen cases (cases 3, 4, 7, 8, 11, 12, 15, 16 and 17) went to autopsy, the notes on the pathologic material of many of them are so brief that it is impossible to form any accurate judgment of the appearance of the various tissues. An attempt at tabulating such incomplete data might lead to erroneous conclusions. The abnormalities most frequently noted concern the liver and kidneys.

The liver of our patient showed central necroses, these were also present in cases 4, 8 and 16 and probably in case 7. The liver was not commented on in cases 11, 15 and 17, in case 12, there was a pre-existing nodular cirrhosis.

The changes in the kidneys were discussed at some length by all who reported on autopsies. Aside from the interstitial cellular infiltration, which was noted in six cases, and the dilatation of the glomerular capsules, which was noted in five, the striking abnormality seems to have occurred always in the tubules. Dilatation of the convoluted tubules was commented on in five cases and degenerative changes of some sort in the tubular epithelium were noted in every case. In all except case 4, the lumina of the tubules seem to have been filled with a peculiar material which was always scarce at the more proximal levels, but which was conspicuously abundant in the collecting tubules. In case 8, this substance was referred to as "masses" of hemoglobin, in case 11, as masses of brownish pigmented material, in cases 7 and 12, as masses and granules of eosin-staining material, in case 15, as masses, lumps and granules of an "isotropic substance of the color of brown sugar," and in cases 16 and 17 as yellowish-brown material. The most unusual feature of our case seems to have been the extreme degree of

epithelial necrosis In none of the other cases was calcification noted, and in only one (case 17) was epithelial regeneration noted Attention was not directed to the occurrence in the intact epithelial cells of droplets similar to the pigmented material found free in the tubular lumina Yorke²⁶ gave an excellent description of exactly similar droplets in the renal epithelial cells (*a*) of dogs that died during the passage of hemoglobin resulting from infection with *Plasmodium canis* and (*b*) of rabbits four hours after the intravenous injection of hemoglobin Yorke said of these droplets that there was "but little doubt that they are derived, in part, at least, from hemoglobin"

On the basis of our own observations at autopsy (case 3), which seem to agree in general with the observations of others, we feel justified in saying that the renal disease is of an unusual type It is characterized chiefly by edema and cellular infiltration of the interstitial tissue, dilatation of the intracapsular spaces of the glomeruli, dilatation of the convoluted tubules, advanced necrotic changes in the tubular epithelium, especially that of the collecting tubules, with deposition of pigmented droplets in many of the cells and finally, the appearance in the tubular lumina of leukocytes, large phagocytic wandering cells, desquamated epithelium and peculiar pigmented globules of various sizes Studies of the droplets in the epithelial cells and of the larger pigmented masses in the lumina of the tubules invite the suggestion that they are hemoglobin products of some sort The droplets seen near the glomerular extremity of the tubule possess the staining characteristics of the hemoglobin that is contained in adjacent erythrocytes, but those which occur further down toward the renal pelvis have lost their eosinophilic and fuchsinophilic qualities and show increasing amounts of brownish pigmentation Except for the occurrence of this pigment, the changes in the kidney are much like those found after poisoning with mercuric chloride Hemorrhages into the mucous membranes were noted in four cases

COMMENT

From personal study of the complete records of three cases and from the available information concerning fourteen others reported in the literature, we are led to believe that the characteristic delayed reaction following transfusion described here is dependent on the injection of incompatible blood²⁷ Furthermore it would seem that most of the signs

²⁶ Yorke, W The Passage of Haemoglobin through the Kidneys Ann Trop Med **5** 401, 1911

²⁷ It is important to note that Ottenberg and Johnson (Hitherto Undescribed Anomaly in Blood Groups, J Immunol **12** 35, 1926) found that the incompatible type of reaction may occur even when the donor and recipient are of the same blood group

and symptoms by which the reaction may be recognized develop from the severe functional damage that the injected blood inflicts on the kidneys. That there is an adequate anatomic basis for this functional derangement is clearly shown in autopsy material from cases in which the reaction resulted fatally. When the descriptions are sufficiently detailed to permit analysis, one is struck by the similarity of the renal lesions in all cases. The kidneys are swollen, there are degenerative changes in the tubular epithelium and the tubules are filled with blood cells, desquamated epithelium, blood pigment and debris.

The observed facts seem simple enough. A person receives incompatible blood, as a result of which the kidneys are severely damaged and in due course of time uremia sets in. When we attempt to explain the mechanism by which the incompatible blood damages the kidneys, we find difficulty in arriving at a satisfactory conclusion. Four possible explanations are: 1. By mechanical blockage of their tubules, the kidneys have been rendered functionless as excretory organs. 2. The kidneys are sensitive to certain bodies contained in the injected blood and the functional decline results from a local reaction which is of the nature of an anaphylactic shock. 3. The immediate transfusion reaction brings about a metabolic disturbance that affects renal function. 4. By the action of toxic substances set free in the blood at the time of transfusion, the functioning renal tissue is so severely damaged that it is unable to perform its duties. Each of these possibilities will be given brief consideration.

The conception that renal insufficiency following transfusion may be explained by mechanical blockage of the tubules dates back at least as far as Ponfik³ who was among the first to observe blood pigment casts in the kidneys of dogs that had been given transfusions with incompatible blood. Those who support this view point to the fact that the urinary suppression dates from the outpouring of large quantities of hemoglobin in the urine. Thus far, however, there is no convincing proof of the fact that the casts found in the renal tubules during hemoglobinuria are responsible for the decline in urinary output. Nor indeed, is there sufficient evidence to say that hemoglobinuria *per se* alters in any way the function of the human kidney. It is apparently true that hemoglobinuria in rabbits (Lévy,⁴ Yorke and Nauss,²⁸ Baker and Dodds¹³ and others) may produce renal insufficiency with anatomic changes much like those described in human beings. Bayliss,²⁹ however, who studied the subject in other animals observed that injections of

28 Yorke, W., and Nauss, R. W. The Mechanism of the Production of Suppression of Urine in Blackwater Fever. *Ann Trop Med* 5:287 1911.

29 Bayliss, W. M. Is Hæmolysed Blood Toxic? *Brit J Exper Path* 1:1 (Feb.) 1920.

hemolyzed blood are "innocuous to the cat and dog" What is more significant, Sellards and Minot³⁰ injected sufficient quantities of hemoglobin into human beings to produce marked hemoglobinuria without appreciably affecting renal efficiency It is noteworthy that in the latter experiments it seemed to make no difference whether the hemoglobin was derived from blood of the same or of an incompatible group Dr A R Rich,³¹ who conducted similar investigations on human beings in the Johns Hopkins Hospital, arrived at the same conclusion that the injection of hemoglobin in sufficient amounts to produce marked hemoglobinuria is a harmless procedure Considering the matter from another point of view, it is significant that in several of the cases in which urinary suppression followed transfusion, hemoglobinuria was not noted There is therefore no substantial reason for regarding the hemoglobinuria and the blood pigment casts as the direct cause of the renal insufficiency Despite this, the histologic observations in the kidneys, previously described, make the theory still somewhat attractive

The second possibility, that the kidneys are sensitive to a substance contained in the incompatible blood and that the renal insufficiency results from a reaction of the nature of an anaphylactic shock, finds its chief support in the associated clinical phenomena, the urinary suppression dates from a generalized reaction resembling anaphylactic shock The fact that anaphylactic shock in the spontaneously hypersensitive person may be associated with a temporary but severe grade of renal insufficiency has been pointed out by Longcope and Rackemann³² After three days on a diet containing considerable beef, one of their patients who was markedly sensitive to beef serum suddenly had an attack of urticaria Studies of renal function before, during and after the attack showed that during the attack there was marked albuminuria and cylindruria with retention of water, chlorides and nitrogen and a precipitate fall in phthalein excretion It is conceivable that this reaction could occur in a person who is hypersensitive to the substances contained in incompatible blood³³

In discussing the third possibility, that the immediate transfusion reaction brings about a metabolic disturbance which affects renal function, we wish to consider particularly the salt metabolism It is a well

30 Sellards A W and Minot, G R Injection of Haemoglobin in Man and Its Relation to Blood Destruction, with especial Reference to the Anaemias, *J M Research* **34** 469 1916

31 Rich, A R Personal communication to the author

32 Longcope, W T, and Rackemann, F M Severe Renal Insufficiency Associated with Attacks of Urticaria in Hypersensitive Individuals, *J Urol* **1** 351 (Aug) 1917

33 A more comprehensive discussion of this problem will be found in Lindau's article (footnote 5)

recognized fact that loss of chlorides as a result of persistent vomiting may be considerable. Associated with this loss of chlorides there is at times a remarkable nitrogen retention with clinical phenomena simulating the uremia of progressive renal disease. Bennett³⁴ has considered such conditions under the heading "Renal Disease of Gastric Origin." Whether there is actually a specific renal lesion accompanying the fall in chlorides is still an unsettled point. Brown, Eusterman, Hartman and Rowntree,³⁵ and Zeman, Friedman and Mann³⁶ described a severe grade of tubular nephritis in cases of pyloric obstruction in which persistent vomiting was followed by nitrogen retention and uremia. Blum and his associates in a great number of publications have recently contributed much to an understanding of this condition which they term "l'azotémie par manque de sel." They feel that the azotemia is not due primarily to a renal lesion, but that it is a compensatory mechanism resulting from loss of chlorides.³⁷ They describe the occurrence of this hypochloremic azotemia in a variety of conditions: (a) vomiting due to pyloric obstruction, (b) vomiting of unexplained origin,³⁸ (c) prolonged diarrhea,³⁹ (d) diabetic acidosis⁴⁰ and (e) nephritis with vomiting and restriction of the salt intake.⁴¹ In going over our cases of transfusion, discussion arose as to whether we might be dealing with an azotémie par manque de sel. This was suggested by the facts that the nitrogen retention almost always followed a period of persistent vomiting, and that tetany—possibly gastric tetany—was described in two of the cases. It seems possible that loss of salt contributed to the symptomatology of some of the cases, but that it was not the most important factor seems clear to us from the following facts: (a) The edema that was present in a fair proportion of cases, and was extreme

34 Bennett, T. I. Goulstonian Lectures on Some Problems of Nephritis (Lecture I), *Lancet* **1** 535 (March 17) 1928.

35 Brown, G. E., Eusterman, G. B., Hartman, H. R., and Rowntree, L. G. Toxic Nephritis in Pyloric and Duodenal Obstruction. Renal Insufficiency Complicating Gastric Tetany, *Arch. Int. Med.* **32** 425 (Sept.) 1923.

36 Zeman, F. D., Friedman, W., and Mann, L. T. Kidney Changes in Pyloric Obstruction, *Proc. New York Path. Soc.* **24** 41, 1924.

37 Blum, L., Grabar, P., and van Caulaert, C. L'azotémie par manque de sel. Son mécanisme, *Ann. de méd.* **25** 34 (Jan.) 1929.

38 Blum, L., Grabar, P., and van Caulaert, C. Phénomènes d'hypochloruration apparaissant chez un urémique traité par le régime sans sel, *Bull. et mem. Soc. méd. d'hôp. de Paris* **53** 251 (Feb. 25) 1929.

39 Blum, L., and Weil, J. Entérite aiguë avec état comateux et forte azotémie, *Bull. et mem. Soc. méd. d'hôp. de Paris* **52** 1620 (Dec. 6) 1928.

40 Blum, L., Grabar, P., and van Caulaert, C. L'azotémie par manque de sel dans le diabète grave, *Ann. de méd.* **25** 23 (Jan.) 1929.

41 Blum, L., van Caulaert, C., and Grabar, P. Les différents types de néphrites avec azotémie. Leur diagnostic différentiel, *Presse méd.* **37** 90 (Jan. 19) 1929.

in several, is not a feature of the hypochloremic azotemia (b) In case 2, the only case in which the blood chlorides were adequately followed, there was no hypochloremia The following tabulation shows the blood nonprotein nitrogen and blood chlorides (chloride as sodium chloride in the whole blood filtrate) in milligrams per hundred cubic centimeters in case 2

	Feb 2	Feb 3	Feb 7	Feb 9	Feb 13
Sodium chloride	532	532	548	564	577
Nonprotein nitrogen	147.8	150	60.3	46.2	32.4

The fourth possibility, that the anatomic and functional renal changes are brought about by irritating or toxic substances contained in the incompatible blood, is rendered plausible by the character of these renal changes The edema of the kidney, the infiltration with wandering cells, and the necrotic tubular epithelium suggest an acute poisoning of some sort Goormaghtigh,⁶ in describing the kidneys of his patient (case 4), noted that they presented the picture of a toxic tubular nephritis He considered the associated liver necroses as additional evidence for the theory that the whole reaction is due to a toxic process The frequency with which liver necroses form a part of the pathologic picture is striking, and is a strong point in favor of this theory Just what portion of the injected blood is capable of such toxic action it is difficult to say Levy,⁴ who investigated this subject, came to the conclusion that the hemoglobin was the portion of the blood which damaged the tubular epithelium Levy's experiments however, were on rabbits and, as noted, more recent work seems to show that hemoglobin is innocuous to man (In this connection it is interesting to note that in the descriptions of blackwater fever [Dudgeon⁴²], one finds a picture similar to that of the transfusion reaction a febrile paroxysm followed by hemoglobinuria, urinary suppression, vomiting, jaundice and, at autopsy, liver necroses and renal lesions not unlike those already described As the patient recovers, the evidences of nephritis clear up rapidly It is sometimes stated that the renal lesions of blackwater fever are due to the hemoglobinuria per se, but I can find no convincing proof of this Lindau⁵ commented at length on the similarity of the delayed transfusion reaction to blackwater fever He also called attention to renal lesions in human paroxysmal hemoglobinuria and in the various hemoglobinurias of animals) In short, though it cannot be said that any particular part of the incompatible blood is responsible, the changes in the kidney and liver are of such a character as to make tenable the conception that they are brought about by an irritating or toxic substance set free in the blood at the time of transfusion

⁴² Dudgeon, L Blackwater Fever, *J Hygiene* **19** 208 (Oct) 1920

Of course it is difficult to say whether one or a combination of the foregoing possibilities accounts for the occurrence of uremia after transfusion. The fourth suggestion might explain the observations in the three cases that have come under our own observation but as we have followed only three of the seventeen cases we hesitate to apply this explanation to the entire series. It has not been our purpose to explain we wish rather to characterize what seems a clearly defined and probably not an uncommon type of reaction following transfusion.

Finally the fact should be emphasized that careful estimation of the daily output of urine will aid much in foretelling the ultimate outcome in these cases. It is well to remember that after an immediate reaction following transfusion the occurrence of the more dramatic hemoglobinuria is of far less prognostic significance than the amount of urinary excretion.

SUMMARY

1 A delayed or prolonged reaction following transfusion is described in seventeen cases. Of these cases three are reported for the first time and fourteen have been gathered from the literature.

2 The reaction generally runs a peculiar and highly characteristic course which presents the following features: (a) Immediately after transfusion there is a sharp febrile reaction followed frequently by hemoglobinuria and invariably by suppression of urine. (b) There is an interval of several days during which there is symptomatic improvement but continued oliguria. (c) After this interval the characteristic features of the delayed reaction develop rapidly. They usually begin with agitation or drowsiness which is replaced by outspoken evidences of uremia. Convulsions and coma may supervene.

3 The outcome is frequently fatal: eleven of the seventeen patients died. Recovery is associated with diuresis: death occurs in uremia.

4 At autopsy the kidneys are swollen: the tubular epithelial cells contain droplets of a peculiar pigmented material and show advanced degenerative changes: the tubular lumina are filled with various cells, blood pigment and debris. Small necroses are generally found in the liver.

5 The events may be summarized as follows: A subject receives an injection of incompatible blood: his kidneys are severely damaged and in due course of time uremia sets in. Several possible explanations of these events are discussed.

6 The delayed reaction is not rare: beside the seventeen cases discussed in detail a number of cases in the literature are cited.

THE MECHANISM OF THE EPIGASTRIC DISTRESS ASSOCIATED WITH AN IRRITABLE COLON AND CHRONIC APPENDICITIS

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AND

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The epigastric distress due to extragastric lesions may so closely resemble that due to peptic ulcer that a detailed study is necessary for the differentiation. The present study is concerned with the mechanism of the epigastric distress associated with a spastic colon and chronic appendicitis. The fundamental factors responsible for the epigastric distress in these conditions are no doubt common to conditions caused by other extragastric lesions. Clinical observations¹ indicate that the discomfort is induced by a stimulation of the stomach. In a former investigation² a reflex stimulation of the stomach from the colon appendix and gallbladder was demonstrated in the dog. The introduction of a few drops of croton oil in the proximal colon was usually followed by an increase in tone and a striking increase in the peristaltic action, particularly of the pyloric portion of the stomach. When the irritation was confined to the appendix or applied to the mucosa of the gallbladder, the same gastric phenomenon was observed. In each instance the stimulating effect on the stomach was promptly abolished by atropine.

These observations directed our attention to the study of the tone and peristaltic action of the pyloric section of the stomach in patients with a spastic condition of the colon and localized recurring epigastric distress. Patients were selected in whom it was possible to induce the typical epigastric distress by injecting air into the colon through a rectal tube. The quantity of air was measured and varied from a few cubic centimeters to 1,000 cc. Ordinarily, 500 cc or less was effective. In some

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1 Smith, Fred M., Miller, G. H., and Fowler, W. M. The Gastric Manifestations Associated with a Spastic Colon, *J. A. M. A.* **93** 1932 (Dec 21) 1929

2 Smith, Fred M., and Miller, G. H. A Study of the Reflex Influence of the Colon, Appendix and Gallbladder on the Stomach, *Arch. Int. Med.* **46** 988 (Dec.) 1930

instances the distress was produced by massaging an suitable section of the colon, particularly the ileocecal region. We were interested in the registration of the gastric activity of the pyloric portion of the stomach. A rubber condom was selected for this purpose. This was anchored in the pylorus by an Einhorn bucket which was attached to a piece of small rubber tubing, extending for from 3 to 4 inches (7.62 to 10.16 cm) below the lower end of the condom. The position of the balloon was checked in several instances by fluoroscopic examination. After the balloon was passed into the stomach, the patient lay on the right side until it was engaged in the pyloric region. The balloon was then connected with the bellows recorder, and a control record of the gastric activity was obtained on the kymograph. Air was then introduced into the colon by means of a rubber bulb through a rectal tube. There was at once a striking increase in the tone, an onset of more active peristalsis and the appearance of the typical epigastric distress. The pain corresponded with changes in tone or the passage of a peristaltic wave.

REPORT OF CASE

The following report is indicative of the type of patient selected for investigation and illustrates the method of study.

CASE 1—F. W., aged 45, was admitted to the medical department of the University Hospital in July, 1929. He complained of recurring epigastric distress, which had been appearing at intervals over a period of ten years. The distress was localized slightly above and to the right of the umbilicus and was described as a feeling of fulness or a gnawing sensation. It appeared from one to three hours after meals and was more apt to follow the evening meal. There was frequently nausea and vomiting during severe distress, which was followed by complete relief. The discomfort was also relieved by belching and the passage of gas by bowel. The epigastric pain was often associated with distress, particularly in the right lower quadrant, and the consciousness of gas in the lower part of the abdomen. It was noticed that the pain was more apt to be present during periods of constipation, which were occasionally followed by diarrhea. The patient was more liable to have a severe attack of epigastric pain when the stools were scybalous. The gallbladder and appendix had been removed in 1925. Apparently neither of these structures had been significantly diseased. There was relative freedom from the discomfort for two and one-half years following the operation. During the months preceding admission to the hospital the distress was more severe and appeared at more frequent intervals. There was no history of hematemesis or melena.

Examination revealed tenderness in the right lower quadrant. The secretory function of the stomach was regarded as normal. Roentgen examination of the stomach gave negative results. There was a moderate spasticity of the colon. The introduction of air into the colon was followed by discomfort in the right lower quadrant and the appearance of typical epigastric distress.

A balloon was passed into the stomach and allowed to engage in the pyloric portion. It was then connected with a kymograph, and after a control record was obtained, air was introduced into the colon. Immediately following the injec-

tion of the air there was a change in tone, the stomach became active and the patient experienced the typical epigastric distress. The patient was taught to register the periods of distress. This distress corresponded with the peristaltic waves. It appeared during the upstroke and subsided on the downstroke. Following the administration of atropine, there was a gradual reduction in the tone of the stomach, and after a few minutes the peristaltic waves ceased and the pain disappeared. The gastric activity subsequent to the full effects of the atropine was similar to that during the control period.

A few days following the aforementioned experiment, a fluoroscopic examination of the stomach was again made. During the examination, air was introduced into the colon. The patient at once experienced distress. It was localized over the pylorus and occurred as a peristaltic wave passed over the pyloric ring. The distress in each instance disappeared as the wave passed and returned with the subsequent wave.

CASE 2—The record in figure 1 is from another patient with a recurring localized distress, which occurred at from one and one-half to two hours after meals. Relief was obtained by taking soda, by belching, by the passage of gas by bowel and by bowel movement. This discomfort had appeared periodically for from four to five years and was more apt to be present during periods of constipation. In the gastro-intestinal examination, a spastic colon was the only significant observation. A rectal tube was passed, and as soon as air was introduced into the colon, the typical burning sensation was felt in the epigastrium. This distress was also induced by the massage of the ileocecal region, and the possibility of chronic appendicitis was considered. The internal inguinal rings were large, and a definite bulging was noted on coughing. The stretching of these rings by the fingers also produced the pain in the epigastrium.

In the gastric curve (fig. 1) there was a striking increase in tone, and the stomach at once became active. After the inflation of the colon the registration of the pain was done in the usual manner and is indicated below the gastric curve. The pain corresponded to the increase in tone or the passage of a peristaltic wave. In this experiment the influence of nitroglycerin was tested, and there was no apparent change following the first administration. After the second dose, however, there was a sharp reduction in tone and a decrease in the size of the peristaltic waves, but the epigastric distress continued. After a few minutes atropine was administered, with a subsequent reduction in tone, cessation of peristalsis and the disappearance of the pain.

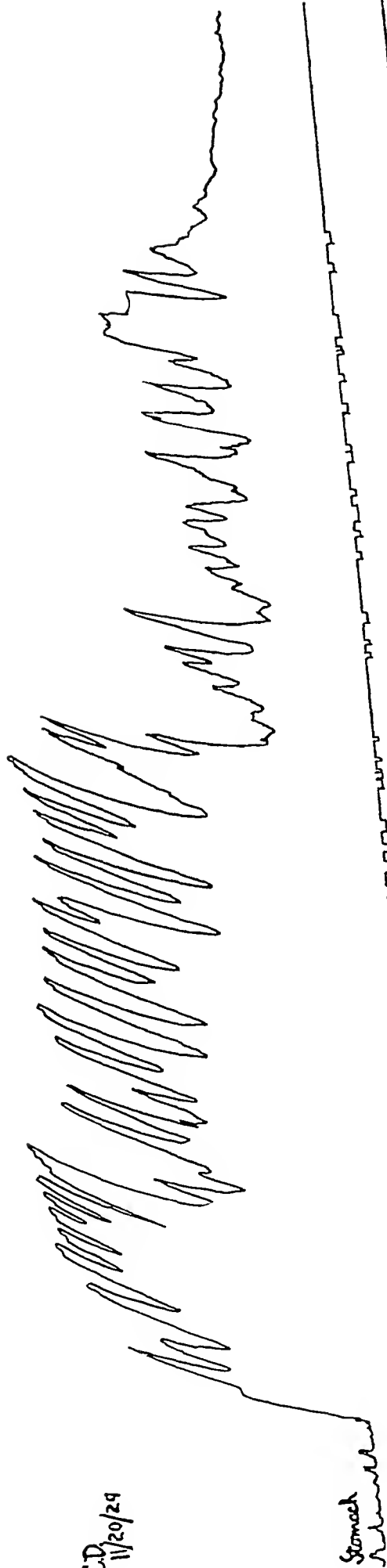
These observations indicated marked changes in the stomach following the introduction of a small quantity of air into the colon. This feature was checked by a fluoroscopic examination. The position and activity of the stomach was carefully observed, and then air was injected into the colon. There was at once a striking increase in tone, and the stomach assumed a higher level and became active. A prepyloric spasm was noted, and the typical pain was localized over this area. This pain was intermittent and continued to be localized over the spasm, regardless of the change in the position of this region of the stomach.

The patient was transferred to the department of surgery for the repair of the hernia and removal of the appendix. There was, however, no significant pathologic process in the appendix.

The following case is of particular interest because of the delayed response to the injection of air into the colon.

CASE 3—This patient was well until five months prior to examination in December, 1929. He began to notice a gnawing pain in the epigastrium that

C.D.
11/20/29



Atropine SO_4
0.013 gm
(intravenous)

Nitroglycerine
0.0045 gm
(mouth)

Nitroglycerine
0.0086 gm
(mouth)

Colon Inflated

One min.

Each registration of the gastric curve. Each registration of the time marker represents one minute. The appearance of the epigastric peristalsis and the appearance of the epigastric tone. The stimulation effect on the tone. The onset of an active peristaltic wave or a change in tone. The administration of atropine.

Fig 1—The appearance of pain is recorded on the line below the gastric curve. The introduction of air into the colon was followed by an increase in tone, the onset of a peristaltic wave and later abolished by the administration of nitroglycerin and later abolished by the administration of atropine. In each instance the occurrence of the pain corresponded with a peristaltic wave of the stomach was diminished by the second administration of nitroglycerin and later abolished by the administration of atropine.

occurred two to three hours after meals. This distress was relieved by the taking of food and soda. There was an occasional sensation of pressure throughout the entire abdomen. The bowels were inclined to be constipated, and since the onset of the illness the stools were frequently scybalous. It was during this period that the distress was most frequently experienced in the epigastrium. On the other hand, if the stools were formed and of good size, there was relative freedom from the pain. The free acid of the gastric content was relatively low. Roentgenologic examination of the stomach showed a prepyloric spasm, but no evidence of ulcer.

After the registration of a control period of the gastric activity, air was introduced into the colon in quantities of 500 cc, on two occasions, without any apparent alteration in the stomach and without pain (fig 2). Within a few minutes the patient began to experience discomfort over the lower part of the abdomen, with an intense desire to move the bowels. Coincidentally there was an abrupt increase in the tone of the stomach, the registration of tall gastric waves and the appearance of the typical epigastric pain. Later, air was expelled, which was followed by relief from the lower abdominal discomfort, but the epigastric distress continued. In the meantime there was some reduction in the gastric activity. Atropine was then administered, with a subsequent reduction in gastric tone, a cessation of peristalsis and the disappearance of the epigastric pain.

Later, another fluoroscopic examination of the stomach was made and air was introduced into the colon. Coincident with the injection of the air a marked prepyloric spasm was observed, and the typical pain was produced which was localized over the spasm.

The localized epigastric pain associated with a spastic colon could occasionally be induced by palpation of the ileocecal region.

The curve in figure 3 illustrates this feature. The registration on the line below the gastric curve indicates the time when the cecum was massaged. It will be noted that there was a gradual increase in the gastric tone, and the peristaltic waves became more prominent. This alteration in the stomach persisted for a few minutes after the irritation of the cecum was discontinued. Immediately following the initial massage of the cecum a sensation of fulness was felt in the epigastrium. Later, coincident with the large waves, the typical epigastric distress appeared.

The observations on a patient with chronic appendicitis were almost similar to those previously recorded.

CASE 4—A woman noticed a gnawing distress in the epigastrium in February, 1923, about three weeks following the birth of her third child. This distress was located slightly to the right of the midline and above the umbilicus, and usually occurred from two to three hours after meals. It appeared at infrequent intervals, and did not cause any inconvenience until 1925, following the birth of the fourth child. On the fourth day after delivery she had fever, diarrhea and generalized abdominal distress. Two weeks later, on her first day out of bed, she had a severe attack of epigastric pain that extended to the back. After a few minutes the pain was transmitted to the right lower quadrant. Following this severe attack the gnawing pain in the epigastrium occurred at more frequent intervals and was often associated with distress over the lower part of the abdomen, particularly on the right side. Physical examination disclosed considerable tenderness in the right lower quadrant over the region of the appendix. On palpation of the region, the typical epigastric distress was induced. The gastric

D5
4/130



Free HCL 26

Free HCL 32

Stomach

Free HCL 0

Expelled
Air

Atropine SO_4
0.0013 grms.
intaken.

Colony
Injected 1000 cc Air

Free HCL 0

One Minute

The introduction of 500 cc of air on two occasions had no immediate influence on the gastric activity. There was an abrupt change in the patient began to have discomfort over the lower part of the abdomen and a desire to move the bowels. The usual response to atropine gastric activity, and the epigastric distress appeared again. This distress corresponded with the peristaltic waves.

A few minutes later, however, there was an abrupt change in the gastric activity. The usual response to atropine was noted.

W.L.
9/22/29

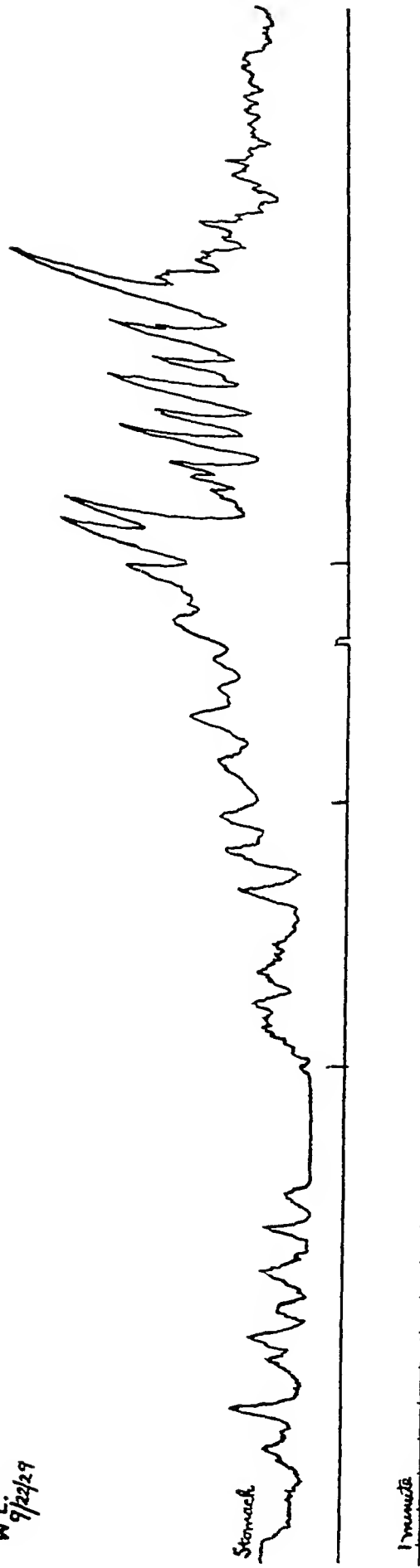


Fig 3—This illustration shows the stimulating effect on the stomach induced by massaging the ileocecal region The registration on the line below the gastric curve indicates the time of the massage

acidity was regarded as normal. Roentgenologic examination of the stomach showed a prepyloric spasm, but no evidence of ulcer. The appendix was visualized during the fluoroscopic examination, and was tender on palpation.

It is to be noted in the gastric curve (fig 4) that pressure over the region of the appendix induced a striking increase in the tone and the peristaltic action of the stomach. Coincident with this change in the stomach, the gnawing epigastric pain was felt. After the administration of atropine the curve returned to that of the control period, and the distress disappeared. The inflation of the colon elevated the registration lever, but no other change was noted, and the distress was not induced. In a later experiment the injection of air into the colon produced changes in the stomach similar to that induced by palpating the appendix, which were also accompanied by distress. There was a prompt response to atropine, even though the air remained in the colon, and subsequent pressure over the appendix had no significant effect.

EB.

12/23/29

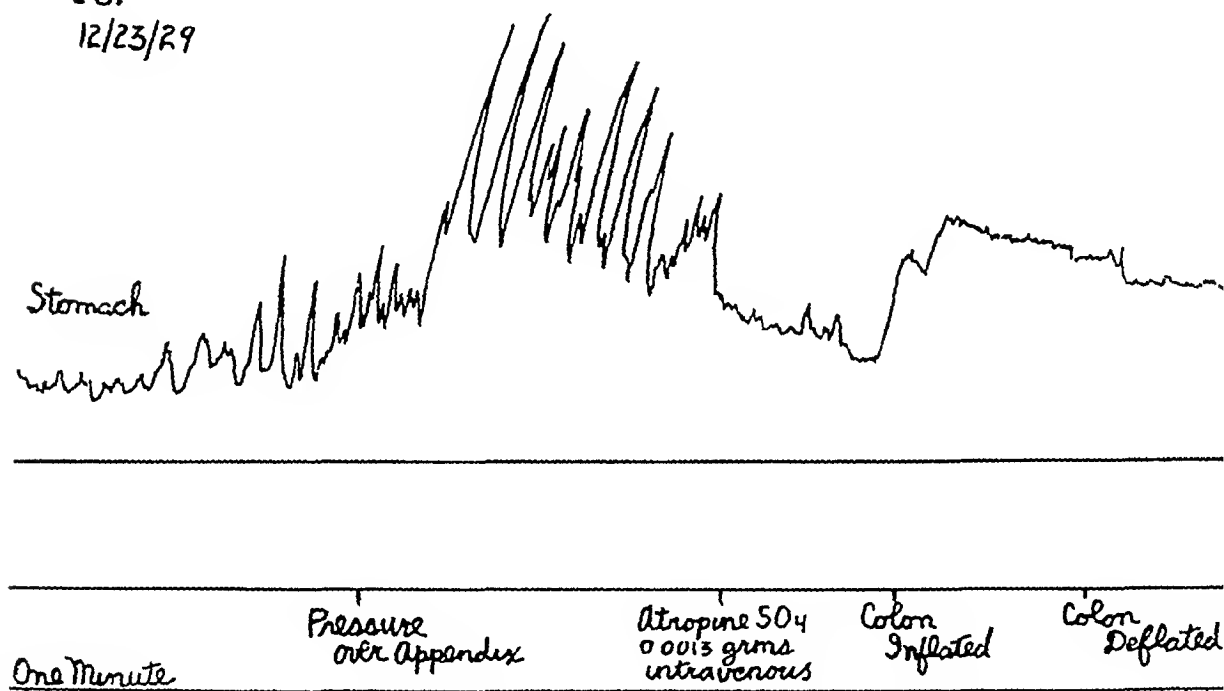


Fig 4—Record of patient with chronic appendicitis. Note the effect of pressure over the appendix. The epigastric distress was induced by the pressure, and corresponded with the peristaltic waves. Following the administration of atropine, the introduction of air into the colon caused some elevation of the writing lever, but had no significant influence in gastric activity.

This patient was later studied by the fluoroscope. The stomach was carefully observed, and then the appendical region was massaged. The tone of the stomach was increased, a prepyloric spasm was noted, and the epigastric pain appeared. It is to be observed that the position of the stomach was changed (fig 5). Air was then injected into the colon. There was a striking change in the position and shape of the stomach, the prepyloric spasm was more evident, and the pain became intense. The pain was localized over the spasm (fig 5C). A picture was taken during pain, and shows the extent of the spasm (fig 5D).

It was felt that possibly a continuous curve of the gastric activity might contribute to the explanation of the periodicity of the epigastric pain. A continuous

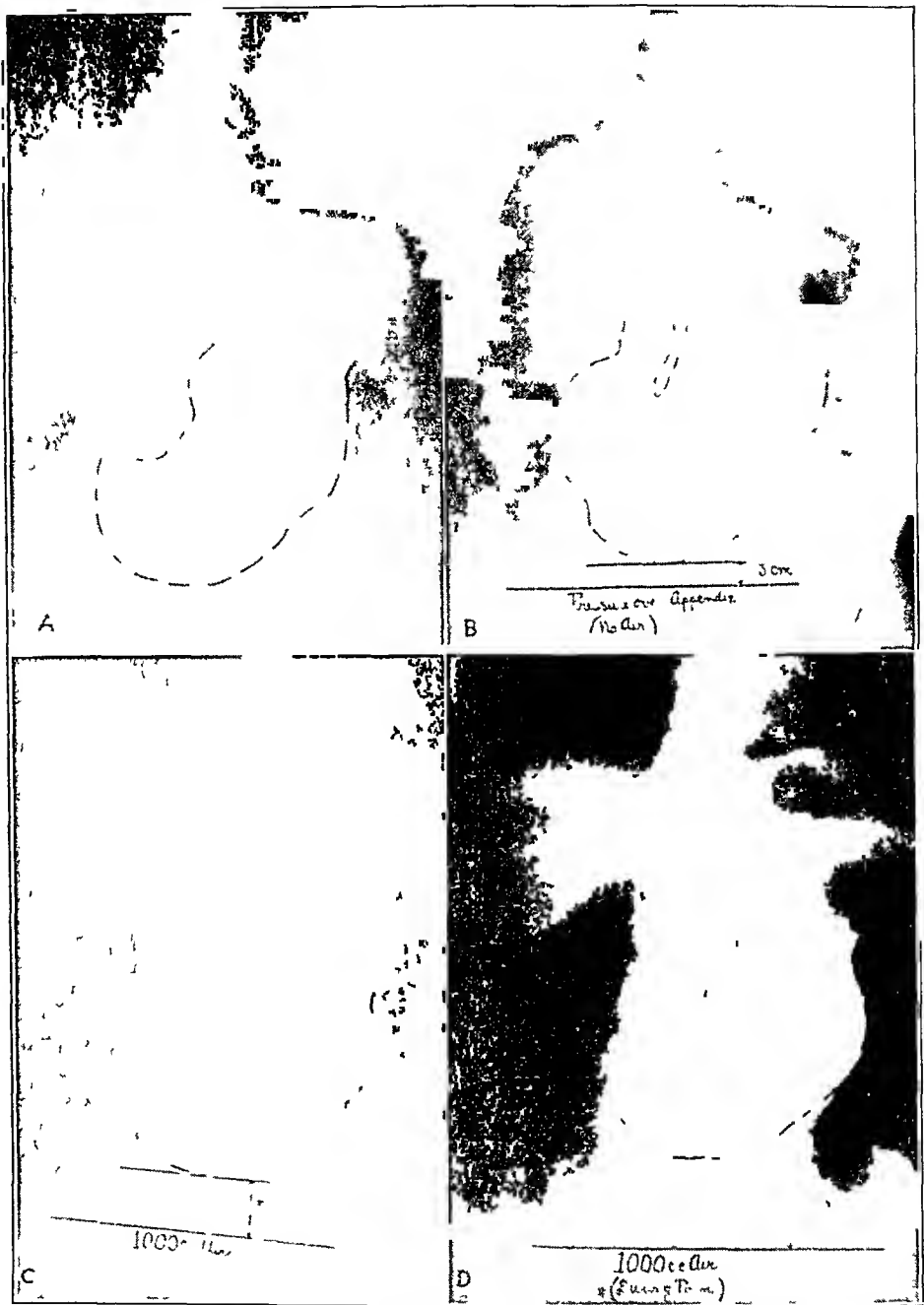


Fig 5—*A*, control roentgenogram, *B*, after pressure was applied over the appendix, *C*, after the introduction of air into colon, note the pyloric spasm, *D*, roentgenogram taken during pain. There was a further elevation of the stomach and the pyloric spasm was more marked. The pain was intense and localized over the region of spasm.

curve was recorded from 8 15 in the morning until 2 15 in the afternoon. The stomach was relatively inactive until about 11 30, and the patient was free from discomfort. There was then a gradual increase in the frequency and depth of the peristaltic waves until 12 30, followed by an abrupt cessation of peristalsis. During the height of the increased peristalsis the gnawing distress was felt in the epigastrium. The pain disappeared with the last large peristaltic wave. About one hour later the cycle was repeated in a minor form. The periods of active peristalsis were regarded as hunger contractions and believed to be related to the production of the pain.

This patient was operated on, and a chronically infected appendix was removed. The diagnosis was later confirmed by the pathologist.

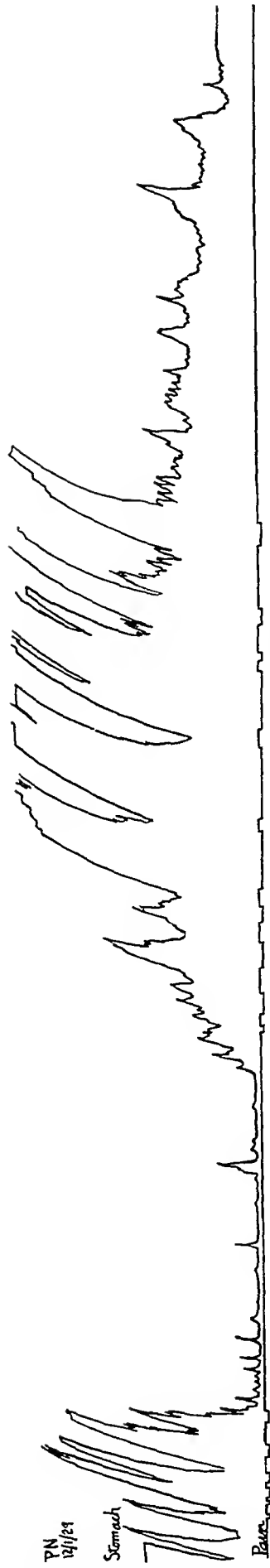
In certain instances of gastric and duodenal ulcers there is a reflex stimulation of the stomach from the colon which contributes to the production of the epigastric pain.

CASE 5—The curve in figure 6 was taken from a patient with recurring duodenal ulcer. The diagnosis of ulcer was first made in 1925. Treatment was instituted in a hospital for two months, and the distress disappeared. The patient was free from symptoms until July, 1929. When the patient was admitted to the University Hospital on Oct. 14, 1929, the clinical and roentgenologic observations were those of a duodenal ulcer. In the beginning of the gastric curve there was active peristalsis, and the typical epigastric pain was felt with each wave. Following the introduction of 30 cc. of a 2 per cent solution of sodium hydroxide into the stomach, there was a cessation of the peristaltic waves, and the pain disappeared. Later, air was injected into the colon with a subsequent increase in pain, and, finally, violent changes in the tone which were accompanied by severe epigastric pain. Amyl nitrite was administered on two occasions without any appreciable influence on the gastric activity or pain. The administration of atropine, however, was followed by a prompt disappearance of the changes in tone and the cessation of pain. The patient stated that the distress induced by the injection of air into the colon was identical with that experienced in the past.

In the majority of the cases of peptic ulcer so far studied, there was no demonstrable stimulation of the stomach from the colon, and the introduction of air into the colon did not induce the epigastric distress. This feature was illustrated in several patients, and in each instance the colon was distended to the point where the patient was exceedingly uncomfortable, yet there was no change in the curve, nor was there epigastric pain.

COMMENT

In the present investigation, a reflex stimulation of the stomach from the colon and the appendix was demonstrated in patients with an irritable colon, chronic appendicitis and peptic ulcer. The stimulating effect on the stomach was manifested by a striking increase in the tone, particularly of the pyloric portion and an increase in the peristaltic action. The same results were obtained regardless of whether air was injected into the colon or the ileocecal region was massaged. In all except one instance, the gastric response was prompt. In this patient



30cc NaOH 2.0%

Colon Inflated

Amyl Nitrite 0.0013 gram in 100cc
 Amyl Nitrite 0.0013 gram in 100cc

Fig 6—Record taken during treatment for duodenal ulcer. During the early period of this record the patient was experiencing the typical epigastric distress which is registered below the gastric curve. Note the effect of sodium hydroxide. Later the colon was stimulated by the introduction of air. A change was at once noted in the gastric curve. The patient again felt an epigastric distress, which he stated was like that experienced in the beginning of the experiment. This pain was again definitely related to the gastric activity. The stimulation of the stomach was eliminated by atropine, and the pain disappeared. Amyl nitrite had no effect.

the introduction of 500 cc of air into the colon on two occasions had no significant influence on the tone or peristaltic action of the stomach. Later, however, when the patient began to experience severe cramps over the lower part of the abdomen, there was an abrupt change in the stomach with the appearance of the typical epigastric distress. The stimulation was apparently not sufficient until the onset of violent peristaltic waves in the colon. The observations in the roentgenologic examination were in accordance with the kymographic records. Alteration in shape and position and frequent marked prepyloric spasm were noted. The results from the kymographic study were more striking, which might be expected from the more delicate means of registration.

Coincident with the onset of the induced alteration in the stomach the typical localized epigastric distress appeared. In each instance the distress corresponded with changes in tone, or with the passage of a peristaltic wave over the pyloric portion of the stomach. This distress was usually intermittent and during active peristalsis it appeared on the upstroke of the lever and subsided on the downstroke. In those instances in which tone changes were the striking feature, the distress persisted until the spasm relaxed. Marked change in tone alone was apparently sufficient to produce the pain, but peristaltic waves, regardless of their intensity, did not seem to be so effective unless opposed by an increase in tone or a spasm of the pylorus. The fluoroscopic observations corresponded with those of the kymograph. The distress was localized over the pylorus, and the external location changed with the shifting of that portion of the stomach. The intermittent pain appeared as the peristaltic wave approached the pylorus, and persisted until the barium sulphate was expelled through the pyloric sphincter. One could predict with a considerable degree of accuracy the exact time of onset and of cessation of the pain. The intensity of the pain seemed to vary with the degree of spasm, and in some instances it was intense. In those instances in which epigastric pain was not induced by the stimulation of the colon, no significant changes were demonstrated in the stomach by either the kymograph or the roentgenologic study.

In the kymographic study the gastric alteration induced by the stimulation of the colon usually subsided after the tension in the bowel was reduced by the expelling of air through the rectum, or was abolished by atropine, even though the air remained in the colon. Amyl nitrite and nitroglycerin were employed in some instances, but they were much less effective than the atropine.

These observations indicate that the epigastric distress of a spastic condition of the colon and chronic appendicitis is gastric in origin, and that it is induced by a reflex stimulation of the stomach. This distress may appear at any time that there is sufficient stimulation of the stomach.

It may occur immediately after meals, particularly when the colon is irritable. There may thus be considerable variation in the time of occurrence, which is one of the features that differentiates this type of pain from that of peptic ulcer. Frequently however, the distress has a definite periodicity that apparently corresponds with the appearance of hunger contractions. The tone and peristaltic action of the stomach is ordinarily greatest at this time. If the tone of the pyloric portion of the stomach is further increased by a stimulation from the colon or the appendix, the epigastric distress appears.

The gastric pain associated with chronic appendicitis and irritable colon may be identical with that caused by peptic ulcer. This type of pain is not dependent on an ulceration of the stomach, nor is it possible for the hydrochloric acid of the gastric content to be a factor. In fact, the free hydrochloric acid is inclined to be low or even absent. The pain induced in patients with peptic ulcer by the stimulation of the colon was said to be identical with that of distress caused by the ulcer. The gastric alterations strikingly resembled those accompanying an irritable colon and chronic appendicitis. The pain also occurred under the same conditions. It would thus seem that the changes in the stomach responsible for the pain in the former condition are probably fundamental in the production of pain in peptic ulcer. A study of the gastric alterations associated with peptic ulcer is in progress and will be reported in a later communication.

CONCLUSIONS

The recurring localized epigastric distress associated with an irritable colon or chronic appendicitis is gastric in origin and is induced by a reflex stimulation of the stomach. The stimulation of the stomach is manifested by an increase in tone, particularly of the pyloric region, and an increase in the peristaltic action. The pain appears to be coincidental with the change in tone and the passage of a peristaltic wave over the pyloric portion of the stomach. The distress may be induced any time at which there is sufficient stimulation of the stomach. It may thus occur immediately after meals or at irregular intervals, but frequently a definite periodicity is observed which corresponds with the appearance of hunger contractions.

In certain instances of peptic ulcer a reflex stimulation of the stomach from the colon was demonstrated, and the typical epigastric distress was induced. The gastric alterations strikingly resembled those associated with irritable colon or chronic appendicitis, and the pain occurred under the same conditions.

In those instances in which epigastric distress was not induced by a stimulation of the colon, no significant changes were demonstrated in the stomach.

ACROMEGALY WITH DIABETES MELLITUS AND XANTHOMA DIABETICORUM

REPORT OF A CASE^{*}

ELAINE P RALLI, M D

NEW YORK

That a decreased carbohydrate tolerance accompanies acromegaly was conclusively shown by Davidoff and Cushing¹. In view of their observations it is not surprising to find the incidence of diabetes mellitus high in this condition. John² reported three cases of this kind, in two of which the onset of acromegaly preceded the onset of diabetes. The fact that pituitary extract has an antagonistic action to insulin³ has brought up the question of whether the diabetes is a true diabetes or the result of an interference with the normal action of insulin. In some cases it would seem that there is a relative, rather than a true, pancreatic deficiency. In others, however, there is little doubt that the diabetes is a true diabetes mellitus, the acromegaly possibly being the original factor in causing the diabetes. Joslin⁴ pointed out that the chromophilic cells of the pituitary exert a partially controlling influence on the cells of the islands of Langerhans, and that in hyperpituitarism the former are increased in number.

The occurrence of xanthoma diabeticorum in severe cases of diabetes was reported by several observers. Outstanding among these was a review of seventy-four cases by Major⁵ in 1924. The tumors are most numerous on the flexor surfaces of the forearms and legs. With this complication there is severe lipemia and a high content of cholesterol in the blood. Major expressed the belief that the disappearance of the tumors is due to the decrease of lipemia and hypercholesteremia. Pathologically, the tumors show fibrosis with an infiltration of small mononuclear leukocytes. The nodules are composed of neutral fat, fatty

^{*} Submitted for publication, June 24, 1930.

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1 Davidoff, L. M., and Cushing, H. Studies in Acromegaly. Basal Metabolism, Arch Int Med **39** 673 (May) 1927.

2 John, H. J. Possible Relationship Between Acromegaly and Diabetes, Arch Int Med **37** 489 (April) 1926.

3 Burn, J. H. J. Physiol **57** 318, 1923.

4 Joslin, E. P. Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928.

5 Major. Bull Johns Hopkins Hosp **35** 27, 1924.

acids and lipoid bodies and contain cholesterol Goldstein and Harris⁶ described the involution of these tumors after six weeks in a patient whom they observed There was a marked flattening of the nodules with loss of color, but the total number did not decrease markedly

The patient in the following case had acromegaly and severe diabetes with xanthoma diabeticorum The acromegaly had persisted since adolescence and had apparently preceded the onset of the diabetes

REPORT OF CASE

An Italian, 37 years of age, was admitted to the hospital on Feb 11, 1930, with the chief complaints of weakness and papules over the whole body The family



Fig 1—The distribution of the tumors on the forearms and the acromegalic character of the hands

history was difficult to obtain, but the patient said that his brother had the same facies The symptoms of polyuria, polydipsia and loss of weight dated back to March, 1929, at which time the patient noted small pinkish tumors on both arms and forearms The patient said that he had felt weaker since the onset and that this weakness had become progressively worse The tumors increased somewhat in size, and he went to a hospital for treatment He was placed on a diet and the tumors disappeared After his discharge from the hospital, however, the tumors reappeared in greater numbers than previously and persisted up to the time of his admission to Bellevue hospital

Physical examination revealed obvious acromegaly (figs 1, 2 and 3) There was an acetone odor to the breath The eyeballs were normal Examination of the chest

⁶ Goldstein and Harris Am J M Sc 73 195, 1927



Fig 2—The distribution of the tumors on the knees

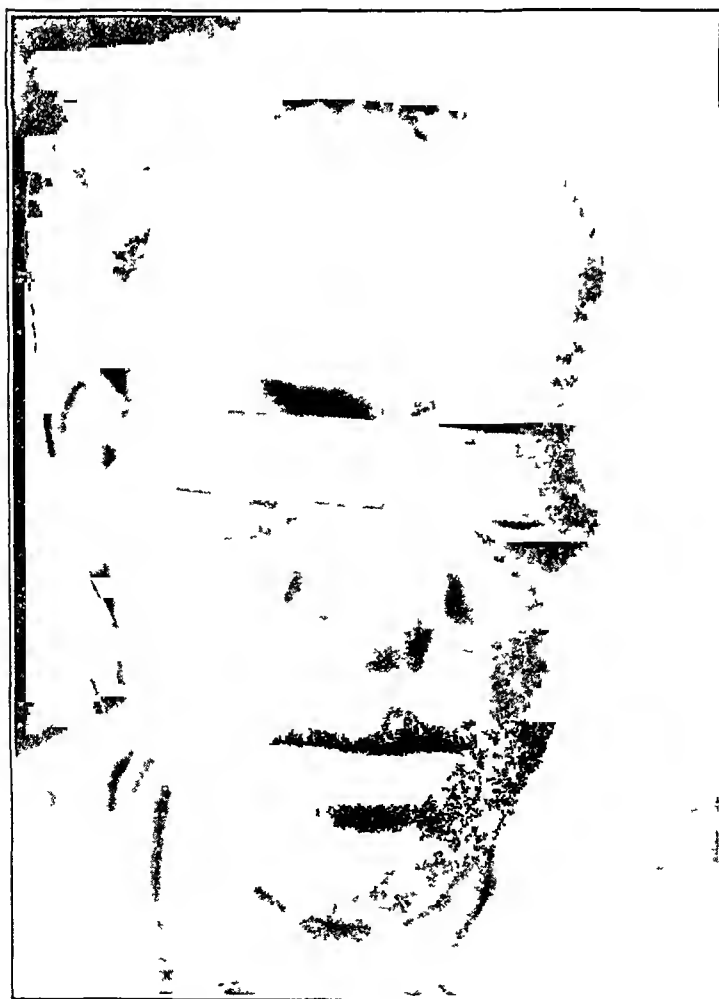


Fig 3—The acromegalic facies

gave negative results. The heart was slightly enlarged, and there were no murmurs. On the outer aspect of both arms, from the wrist to just below the shoulder, but more numerous over the forearms and elbows, there were small tumors varying in size from 0.2 to 0.5 mm. They were also seen over the knees. The growths were firm and yellowish pink. They were not tender or painful. For the most part they were discrete, but over the elbows and knees they tended to coalesce.

Laboratory Observations—The first twenty-four hour specimen of urine showed 48 Gm of sugar, 3+ acetone and 2+ diacetic acid. The blood sugar

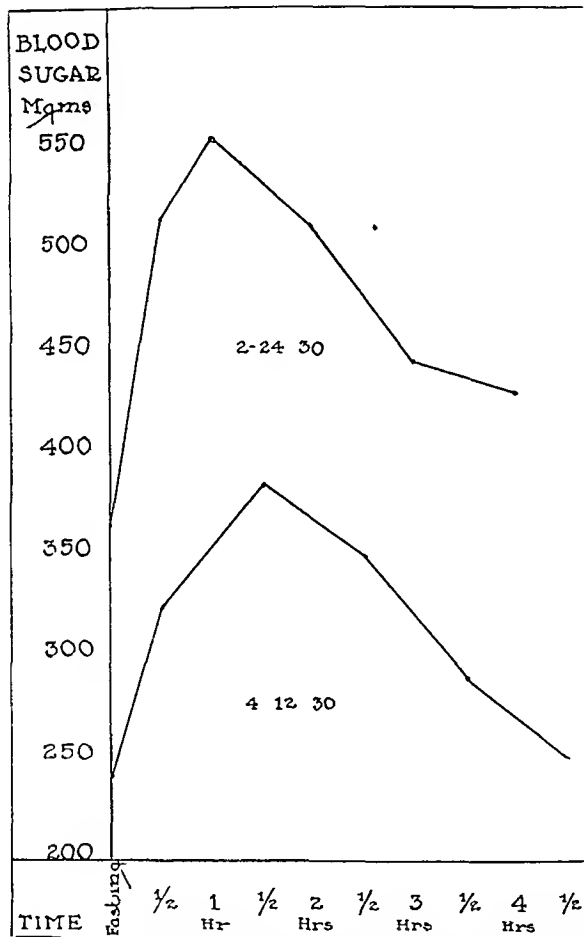


Fig 4—Dextrose tolerance curves obtained on Feb 24 and April 12, 1930

content was 250 mg. The patient was placed on a diet of carbohydrate, 112 Gm, protein, 62 Gm, fat, 127 mg, and a total dose of 35 units of insulin daily. This had practically no effect on the output of sugar, and the urine continued to show sugar for seven days. The insulin was increased to 45 units during this time, but apparently the patient was having food brought to him from outside the hospital. In an effort to gain his cooperation, the carbohydrate in the diet was raised to 140 Gm, the protein and fat remaining the same. At this time the blood sugar content was 300 mg, and the output of sugar 38 Gm a day. The acetone and diacetic acid had disappeared. The insulin was again increased, this time to 70 units, and the patient became sugar-free. The urine still showed sugar occasionally, but the

blood sugar during fasting was considerably lower. Except on two occasions, it remained below 200 mg after glycosuria was controlled. When glycosuria reappeared, the intake of insulin was raised until the condition disappeared again. In this way the patient was kept fairly well under control.

The first estimation of blood cholesterol was made when the blood sugar was at a level of 300 mg, and when there was an average of 40 Gm of sugar daily in the urine. The serum was milky white and typical of extreme lipemia. The cholesterol content of the blood at this time was 5,900 mg. This was determined by the Sackett⁷ method, which is a modification of the Bloor method. It was checked and found to be correct. In reporting the comparative results of cholesterol determinations made by the Sackett method and the Bloor method, Sackett found that the original Bloor method gives a somewhat higher reading. In the university laboratories the normal cholesterol content of the blood, as determined by the Sackett method, was found to average 175 mg. The cholesterol reading for this patient was so high as to deserve mention. After the patient had been sugar-free for two weeks it was found to be 450 mg, at this time the blood serum was normal, and it remained so. The cholesterol was determined on two more occasions, and again was found to be 450 mg, on a third occasion it was 385 mg. The blood sugar at this time was 174 mg. One of the tumors was excised on March 22, at which time the blood cholesterol was 450 mg. This tumor was extracted for cholesterol. The total weight of the sample was 10 mg and it contained 0.8 mg of cholesterol. This determination was also made by the Sackett method.

Two blood sugar curves were obtained—one on February 24 and one on April 12. On both occasions the patient was given 100 Gm of dextrose by mouth. The readings, in milligrams, are as follows:

February 24		April 12	
Fasting	364	Fasting	241
½ hour	526	½ hour	327
1 hour	556	1½ hours	384
2 hours	513	2½ hours	350
3 hours	444	3½ hours	289
4 hours	430	4½ hours	250

These curves obviously point to a severe form of diabetes. The phenolsulphonphthalein test showed a normal kidney function, the total output over a two hour period being 72 per cent.

The urea clearance test for kidney function, according to the method of Møller, MacIntosh and Van Slyke,⁸ gave the following results:

	1st hour	2d hour
U/B ratio*	36.63	43.1
Standard clearance	49.67 cc	57.67 cc
Per cent of normal	91.89	106.7

* $\frac{\text{Urine urea nitrogen}}{\text{Blood urea nitrogen}}$

This showed that there was no impairment of kidney function.

Dr. I. J. Landsman furnished the following roentgen report. The hands showed changes characteristic of acromegaly. Roentgenograms of the skull showed

⁷ Sackett, *J. Biol. Chem.* **44**, 203, 1925.

⁸ Møller, MacIntosh and Van Slyke, *J. Clin. Investigation* **6**, 427, 1928.



Fig 5—Roentgenogram showing the increased size of the sella turcica and the erosion of the anterior and posterior clinoids

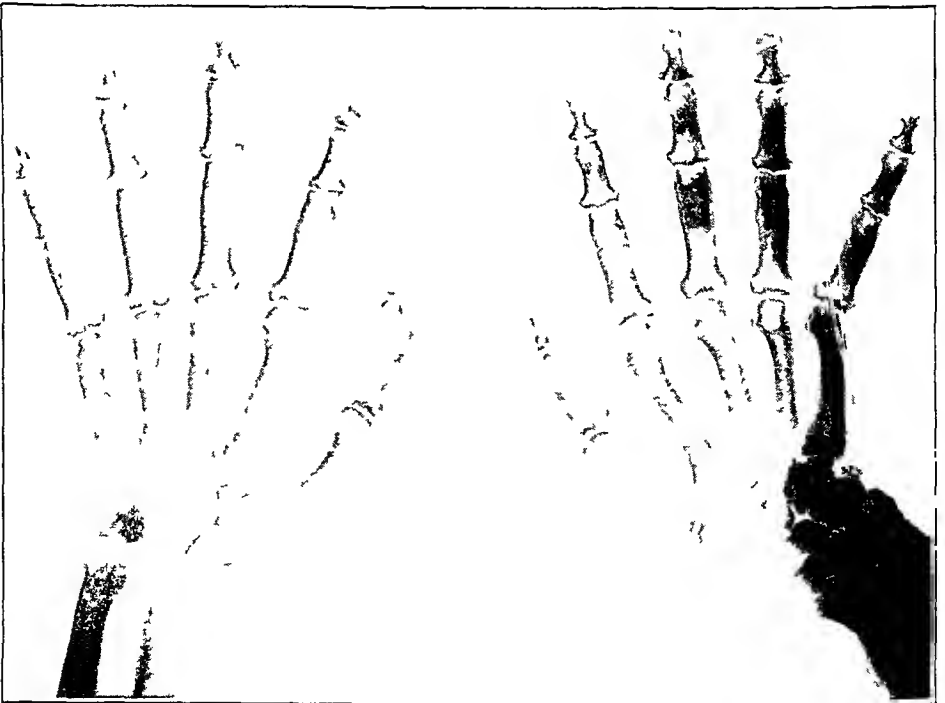


Fig 6—Bones of the hands showing changes characteristic of acromegaly

the sella turcica increased in size, the maximum anterior posterior diameter equal to 20 mm and the height equal to 16 mm. There was definite erosion of the anterior and posterior clinoids. The observations were considered characteristic of a pituitary neoplasm with acromegalic changes.

The photograph of the arms and hands of the patient (fig 1) shows the arrangement of the tumors and the acromegaly of the hand. The tumors are also seen in the photograph of the knees (fig 2), and the acromegalic facies is well demonstrated in the photograph of the patient's head (fig 3). During his stay in the hospital, the tumors were much reduced in size and number but did not entirely disappear. They were distinctly flatter, some being almost flush with the skin. Where they had disappeared, there remained a slight brownish scar.

COMMENT

In view of the fact that the patient had marked acromegaly and showed a definite tumor of the pituitary gland, the severity of the diabetes is not surprising. The hypercholesterolemia and lipemia responded well to insulin and diet, but in spite of this the tumors regressed slowly. The difficulty in keeping the patient continuously sugar-free, even with fairly large doses of insulin, may be accounted for by the increased activity of the pituitary gland. There seems to be little doubt that in this case the diabetes was a true diabetes mellitus, a fact attested to by the presence of the xanthoma, the hypercholesterolemia and the high blood sugar curves.

Book Reviews

A PRACTICAL MEDICAL DICTIONARY By DR THOMAS LATHROP STEDMAN
Eleventh, revised edition Price, \$7.50 New York William Wood &
Company, 1930

This eleventh edition of Stedman's "Medical Dictionary" is of a convenient size and adequately fulfills the requirements of such a book. The primary value of any dictionary, medical or otherwise, is determined in large measure by the author's ability to construct definitions that will be both accurate and concise. In dictionaries of this type one does not expect or desire to find detailed explanations. The author of this work did not lose sight of this fact, and his definitions are well framed and to the point.

Certain devices are introduced which deserve a word of comment because they are the means of conserving time and effort on the part of the inquirer. 1 The definitions are so lucid that a person with little or no medical knowledge is able to understand the meanings at first reading. This quality is of especial importance to students or assistants to physicians. 2 Certain processes, conditions and objects are illustrated, frequently in color. 3 So far as possible, the author has omitted the long lists in the general body of the dictionary. When it has been found necessary to insert such lists, they have been reduced to a minimum by merely giving a name and following this with an asterisk indicating that under the qualifying word the reader will find a more complete description. For example, under the list entitled "test" one finds "Widal's Test." The reader may then find this word in its proper alphabetical order, and in addition to a description of the test, the author has been able to include some biographical data. Had all this information been given in the list it would have interrupted the alphabetical sequence and proved extremely cumbersome. 4 In some cases the author has inserted under the English titles lists in small type which furnish scientific data about the various conditions associated with the parts.

The etymology of the words used in medicine and the formation of terms are compact and clear. The sources of the words are given, Greek sources are given in Roman letters. The author makes the statement that this is done because Greek is no longer generally studied by physicians, as it was in the past. The following example indicates the manner in which this phase is handled. Macrocyte (G makros, large, + kytos cell). The more simple spelling of medical terms has been given preference, the old spellings are given as alternatives.

The appendix furnishes data concerning doses and uses of drugs, weights and measures, stethoscopic abbreviations, temperature and barometer scales, chemical elements and pathogenic microparasites.

On the whole, Stedman's "Medical Dictionary" impresses one as being a highly useful and convenient reference book both for physicians and for laymen who have an interest in medicine.

LES SYNDROMES DOLLOUREUX DE LA REGION EPIGASTRIQUE By RENE A
GUTMANN, Ancien interne des Hôpitaux de Paris, Attache medical de la
clinique chirurgicale de la Salpetriere, charge des consultations des maladies
du foie et du tube digestif Volumes 1 and 2 Price, 200 francs Pp 1093,
with 344 roentgenograms and 198 schematic drawings Paris Gaston Dou

The first volume, covering 520 pages, begins with a general discussion of the symptom, epigastric pain. It then presents the various syndromes and clinical forms of ulcer. Special chapters are devoted to duodenal ulcer, gastric ulcer and juxta pyloric ulcer. Under each of these headings, the clinical picture, together with a detailed description of the roentgen appearance, is given. A chapter on

the treatment for ulcer follows. Gastric carcinoma is dealt with fully, including lymphogranulomatosis, sarcoma and benign tumors of the stomach. The clinical picture, the roentgenologic aspect and the treatment for disease of the gallbladder are similarly set forth.

The second volume begins with a description of the perivisceral syndrome, which is said to be the same for all conditions occurring in the upper part of the abdomen. Pyloric and duodenal stenosis and pyloric insufficiency are next considered. Two hundred pages are devoted to ptosis and dyspepsia, under which are described hyposthenic, orthostatic, hepatic, pancreatic, renal and other even less tangible syndromes. The epigastric distress seen in syphilis and tuberculosis, together with a good description of the organic diseases produced in the upper part of the abdomen by these two infections, is included. The volume ends with a good account of gastrojejunal ulcer, its symptomatology, roentgenologic manifestations, etiology, complications and treatment.

In general, it may be said that the work is thorough. The clinical phases are well presented, being divided into the almost multitudinous forms and syndromes so frequently found in the French literature. The x-ray sections, well illustrated with excellent plates and sketches, are commendable. Very little can be said, however, for the sections on therapy or for the ones dealing with ptosis, kinks, bands, adhesions and dyspepsia. The work is thorough, but frequently not critical.

HISTORY OF HAITIAN MEDICINE. By ROBERT P. PARSONS, LIEUT. COM., M.C., U.S.N. With a Foreword by Edward R. Stitt, Rear Admiral, M.C., U.S.N. Price, \$2.25. Pp. 196, with illustrations. New York: Paul B. Hoeber, Inc., 1930.

This is a highly interesting account of disease in our neighboring Negro-ruled sovereign state of Haiti and the dramatic medical development with the American occupation. So much has been written on the seamy side of Haitian politics and so many aspersions have been cast on this country's efforts by certain factions of the public press that it is refreshing to read of the indisputable achievements of the enthusiastic and scientific medical personnel of the United States Marine Corps and the later organized Public Health Service. The story falls naturally into two parts, Haitian medicine before the American occupation and that following this event in 1915. For centuries after the landing of Columbus in December, 1492, the island remained a plague spot of the earth. A cited author writes that the nosology of Haiti in 1804 would include all the diseases that 312 years of European intercourse would contribute to what the Caribs left before their extermination, together with all that Africa could add in 292 years of slave trade. Smallpox, yellow fever, malaria, yaws, tetanus, voodooism and revolution made life precarious. Yet the population grew. It may be surprising, but it was yaws and not the better known tropical diseases which constituted the major medical problem at the time of the American occupation. This was apparently first appreciated by Dr. Paul W. Wilson of the Public Health Service, who "poured arsenicals into the seething black mass and saw yaws lesions fade away, not in individual cases, but from a whole mountain side." The author holds to the view generally accepted by the medical corps of the military services that yaws is a modified form of syphilis. The style is simple and pleasant, and the volume maintains the high standard of Hoeber's series of books on medical history.

ANATOMY. By GEORGE W. CORNER. Price, \$1.50. Pp. 82, with 8 illustrations. New York: Paul B. Hoeber, Inc.

This book presents in a most scholarly and delightful form a brief review of the development of the science of anatomy from the earliest times. It is one of a series of primers on the history of medicine published by Hoeber under the general title "Chiro Medica." On account of the brevity imposed by the plan, only the most fundamental concepts, discoveries and methods are reviewed. Dr. Corner

has selected these with admirable judgment, and has presented them with a clearness which enables the reader to appreciate their significance. At the end is a brief chapter on current trends in anatomy which indicates the lines along which anatomy is contributing to the advance of the science of human biology.

The trend is toward the study of living tissues from a dynamic or functional point of view. Among the lines along which the advance is being made are cell lineage, the life history of cells, the determination of standards of growth, anthropometry and ethnology. The newer useful methods include tissue culture, the x-rays and photomicrography with moving films. The older methods continue to be useful, for the starting point must always be the dissecting room, and many problems can be solved only with the help of experimentation on animals.

From either literary, scientific or historic points of view, the book will give great satisfaction to all interested in any way in the science of anatomy.

PHYSIOLOGICAL PRINCIPLES IN TREATMENT By W. LANGDON BROWN, M.A., M.D. Cantab, F.R.C.P., Physician to St. Bartholomew's Hospital, with the Collaboration of R. HILTON, M.A., M.B. Cantab, M.R.C.P., Assistant Physician and Assistant Director of the Medical Unit St. Bartholomew's Hospital. Sixth edition. Cloth. Price, \$3.75. Pp. 464, with index. New York: William Wood & Company, 1930.

The popularity of this work is attested to by the appearance of this, the sixth, edition, the first edition appearing in 1908, since which time there have been many changes both in theory and in practice. So many notable changes have occurred in the six years following the appearance of the fifth edition, in 1924, that it has been found necessary to submit the whole book to a thorough revision. The author states, "In retrospect I am struck by two facts. One is the much closer association between physiology and medicine now than twenty-one years ago. The other is that a good indication as to the truth of new work can be gathered from the speed with which its effect is found to be spread beyond its original application. Insulin is an outstanding example of this, instances to the contrary need not be pilloried."

Fundamental discoveries in physiology and clinical medicine are correlated in a clear and interesting fashion, and the application of the principles enumerated therein should have a broadening influence on both student and practitioner.

NERVOUS INDIGESTION By WALTER C. ALVAREZ, M.D., Associate Professor of Medicine, University of Minnesota (the Mayo Foundation). Price, \$3.75. Pp. 284. New York: Paul B. Hoeber, Inc., 1930.

This rather small volume is largely an elaboration of two papers previously written by the author: one on the treatment of nervous indigestion, the other on the effects of emotion on the digestive tract. Its theme is functional rather than organic disease, although some attention is given the latter. There is a brief discussion of the physiology of the gastro-intestinal tract.

It is obvious that the author is chiefly concerned with the care of that large group of patients ill with functional disturbances, commonly classified as "neuroses," who go in despair from one physician to another, and who frequently, failing to find relief, fall into the hands of charlatans of various kinds. The book is interesting and well written and contains much wisdom and sound advice. It will be read with interest and profit by the older, more mature, practitioners, it should be read by all medical students and recent graduates.

The last chapter of thirty-five pages, entitled "Suggestions for Further Reading," contains well chosen paragraphs from the writings of such men as Sir William Osler, Charles Darwin, Oliver Wendell Holmes and S. Weir Mitchell. These selections serve to emphasize the author's central theme—the skilful treatment of functional ills.

ANGINA PECTORIS

THE CLINICAL AND ELECTROCARDIOGRAPHIC PHENOMENA OF THE
ATTACK AND THEIR COMPARISON WITH THE EFFECTS OF
EXPERIMENTAL TEMPORARY CORONARY OCCLUSION

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AND

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WITH THE TECHNICAL ASSISTANCE OF

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Innumerable hypotheses have been proposed to explain the mechanism of an attack of angina pectoris. Huchard¹ collected about eighty such hypotheses in his monograph. It is not within the scope of this paper to enumerate or to discuss the great majority of these. However, the two that seem to be commanding most attention at the present time merit a brief outline.

1 The "coronary hypothesis," stated first by Parry,² holds that the attack of angina pectoris is dependent on a temporary interference with the blood supply of a part of the heart muscle. This hypothesis is based on the following points: (a) the frequency with which advanced coronary disease is found post mortem in patients who have died from angina pectoris³; (b) the similarity of the syndromes of angina pectoris and coronary occlusion in regard to the character and location of the pain; (c) the adequate explanation of the mechanism of sudden death, i. e., ventricular fibrillation and (d) recent experimental work showing that pain can probably be produced by this mechanism.³

* Submitted for publication, May 31, 1930.

From the Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

1 Huchard, H. *Maladies du coeur et des vaisseaux*, Paris, Octave Doin, 1889.

2 Parry, C. H. *An Inquiry into the Symptoms and Causes of the Syncope Anginosa, Commonly Called Angina Pectoris*, Bath, R. Cruttwell, 1799.

3 Singer, R. *Experimentelle Studien über die Schmerzempfindlichkeit des Herzens und der grossen Gefässe und ihre Beziehung zur Angina pectoris*, Wien *Arch. f. inn. Med.* **12** 193 (Feb.) 1926, **13** 156 (Sept.) 1926, **14** 113 (March) 1927. Sutton, D. C. and King, W. W. *Physiologic Effects of Temporary Occlusion of the Coronary Vessels*, *Proc. Soc. Exper. Biol. & Med.* **25** 842 (June) 1928. Sutton, D. C. *Effects of Temporary Occlusion of the Coronary Vessel*;

2 The 'aortic hypothesis,' championed by Allbutt⁴ and Wenckebach,⁵ holds that angina pectoris is produced by distention of the first part of a diseased aorta. This hypothesis is based on the following points: (a) All available evidence seems to be opposed to the possibility that any grave change takes place in the heart muscle during the attack. Irregularity in pulse rate, a drop of blood pressure and signs of heart failure are not integral parts of an anginal attack. (b) Anything that weakens the heart muscle usually tends to prevent angina pectoris. (c) Competent observers⁶ have reported a few carefully studied cases of patients who have died from angina pectoris whose hearts showed no evidence of coronary disease post mortem. (d) Almost all cases of angina pectoris show aortic disease post mortem. (e) Aortic disease (aortitis, rupture, etc.) produces pain, similar in character and distribution to that produced by angina pectoris. (f) Experiments on animals have demonstrated the probable existence of sensory nerve fibers in the aortic adventitia which can give rise to pain if stimulated mechanically.³

It is not certain that all cases of angina pectoris are dependent on one and the same mechanism.⁷ However, the trend of current opinion seems to be toward the belief that the majority of the cases of true Heberden's angina can be explained on a coronary basis. The main difficulty confronting this explanation has been the almost complete lack of direct evidence that the heart is primarily involved during the paroxysm. Recently, data on this point have been supplied by nine cases, reported in the literature, in which attacks of angina pectoris have been studied by means of the electrocardiograph.⁸ All of these

(Proceedings of Central Society for Clinical Research), J Clin Investigation **7** 304 (June) 1929. Percy, J. F., Priest, W. S., and Van Allen, C. M. Pain Due to Temporary Occlusion of Coronary Arteries in Dogs, Am Heart J **4** 390 (April) 1929.

4 Allbutt, Sir Clifford. Diseases of the Arteries, Including Angina Pectoris. London, Macmillan & Company Ltd, 1915.

5 Wenckebach K. F. Toter Punkt ("Second Wind") und Angina Pectoris, Wien klin Wchnschr **41** 1 (Jan) 1928.

6 Osler, Wilham. The Lumlum Lectures on Angina Pectoris, Lancet **1** 697 (March 12) 1910, **1** 839 (March 26) 1910, **1** 973 (April 9) 1910. Levy, R. L. Cardiac Pain. Am Heart J **4** 377 (April) 1929. Romberg, E. Ueber Angina pectoris, Munchen med Wchnschr **76** 797 (May 10) 1929.

7 Wolferth, C. C., and Wood, F. C. Angina Pectoris, M Clin North America **13** 951 (Jan) 1930.

8 Bousfield, G. Angina Pectoris, Changes in the Electrocardiogram During a Paroxysm, Lancet **2** 457 (Oct 5) 1918. Feil, H., and Siegel, M. L. Electrocardiographic Changes During Attacks of Angina Pectoris, Am J M Sc **175** 255 (Feb) 1928. Levy, J. R. Valeur semiologique des alterations du complex ventriculaire electrique dans les syndromes angineux, Arch d mal du coeur **22** 523 (Aug) 1929. Levy refers to other reports on this subject. They were investigated and found not to contain electrocardiographic studies made during the attacks.

cases but one (a case with a mild paroxysm) ' showed a definite change in the ventricular complex during the attack. These electrocardiographic data have been cited by some writers¹⁰ as evidence that all angina is coronary in origin. This inference is not justifiable on the basis of the evidence at hand. Certain questions remain to be answered: 1. Do these electrocardiographic changes occur in every severe attack of angina pectoris? 2. Do they closely parallel the pain? 3. Are they due to some specific change in the heart, such as a temporary myocardial ischemia, or are they merely due to the exercise which provoked the attack or the changes in blood pressure or pulse rate which accompanied it?

ELECTROCARDIOGRAPHIC STUDIES OF ATTACKS OF ANGINA PECTORIS

Thirty cases of angina pectoris were studied with the foregoing problems in mind. In six cases the attacks were spontaneous, in twenty-four cases the pain was induced by varying amounts of prescribed exertion, which was stopped at the first suggestion of pain. Some patients were studied in more than one attack. Whenever possible, electrocardiograms were taken before, several times during, and several times after, each attack. Blood pressure readings were taken at intervals during most of our studies.

The decision as to whether the patient had an attack of "true angina" was not always easy to make. The decision was based on the usual clinical phenomena, the location, radiation and character of the pain, its relation to exertion and rest and the demeanor of the patient during the paroxysm. Doubtful cases were discarded. A study of the tracings that were obtained revealed that all of them showed transient changes in the ventricular complexes during the pain.

In an attempt to rule out exercise and alterations in blood pressure or pulse rate as factors in the production of these electrocardiographic changes, a series of controls was studied. 1. The effect of various amounts of exercise on the electrocardiogram was observed in 100 normal subjects, in 50 patients with cardiovascular disease other than angina (chronic valvular disease, hypertension, defects in conduction, electrocardiographic abnormalities, and myocardial insufficiency) and in 12 patients with histories of anginal attacks in whom the prescribed exertion was not productive of a paroxysm. 2. The effect of paroxysmal pain, known to be due to an extracardiac lesion, was studied in 4 cases (ureteral colic, distended bladder, duodenal ulcer and diaphragmatic hernia).

⁹ Feil (footnote 8, second reference)

¹⁰ Danielopolu, D. *L'angine de poitrine et l'angine abdominale*, Paris, Masson et Cie, 1927. Veil, P., and Codina-Altes, I. *Traité d'électrocardiographie clinique*, Paris, Gaston-Doin et Cie, 1928, p. 387.

It was found that these various control procedures frequently produced profound temporary changes in the ventricular complex of the electrocardiogram, but that these changes were quite consistently of one type¹¹ As a rule, the Q-R-S complexes did not change perceptibly. With exhausting exercise the electrical axis of the heart tended to deviate toward the right (chart 4). The T waves showed the most important alterations. The general rule was that inverted T waves tended to become upright, while upright waves increased in height (charts 1, 2 and 3). There were certain exceptions to this rule. In lead I the T wave was frequently unchanged by exertion, in untrained persons following exercise sufficiently exhausting to produce a definite shift of the electrical axis toward the right, the T wave in lead I sometimes decreased in size parallel to the change in the R wave (chart 4). The only other exception to the general rule formulated was a man,

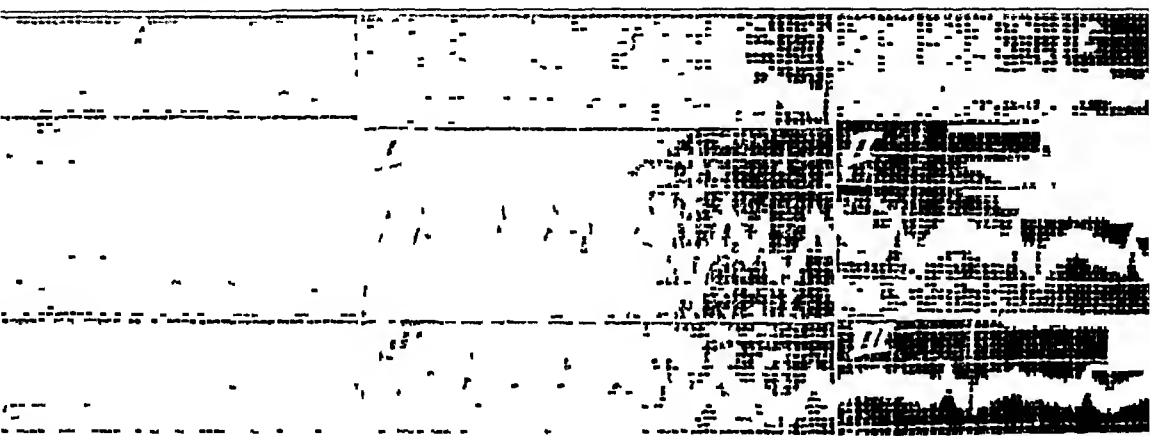


Chart 1—Effects of exercise on a normal student, aged 21. Cardiovascular examination showed no abnormalities, except the slight reduction in size of T_1 . *A* represents the control tracing, *B*, tracing taken immediately after running up four flights of stairs in which marked increase in size of T_2 and T_3 occurred, and *C*, tracing taken five minutes later (practically identical with *A*). The original charts on which this article is based were lost in transit. Seven of them (charts 1, 5, 6, 10, 13, 14 and 15) could not be duplicated from the original electrocardiographic tracings. Therefore they were reproduced from slides which had been made of the original tracings.

aged 32, who had been having "indigestion" in the left hypochondrium and precordial region, but who did not have an attack of pain after exercise. This patient showed a reduction of the T wave in lead II immediately after running up four flights of stairs, and the T wave in lead III, previously 0.5 mm high became slightly diphasic. In none of our control subjects did exercise produce a deepening of an

11 Messerle, N. Die Veränderungen im Elektrokardiogramm bei Körperarbeit, *Ztschr f d ges exper Med* 60 490, 1928.

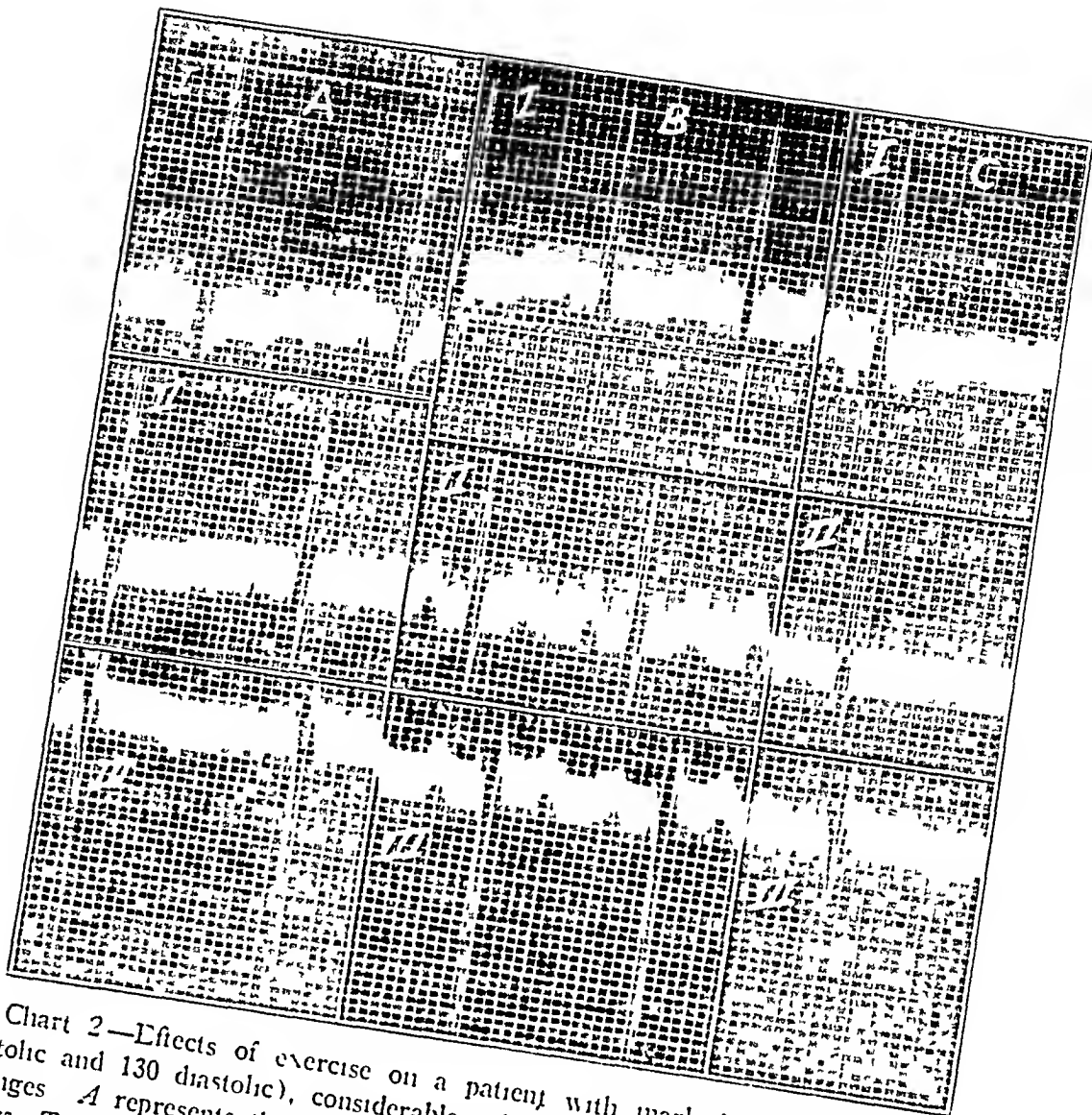


Chart 2—Effects of exercise on a patient with marked hypertension, (220 systolic and 130 diastolic), considerable enlargement of the heart, and T wave changes. A represents the control tracing, B after walking up three flights of stairs, T₁ did not change T₂ and T₃ both became definitely upright, and C that taken five minutes later (similar to 1)

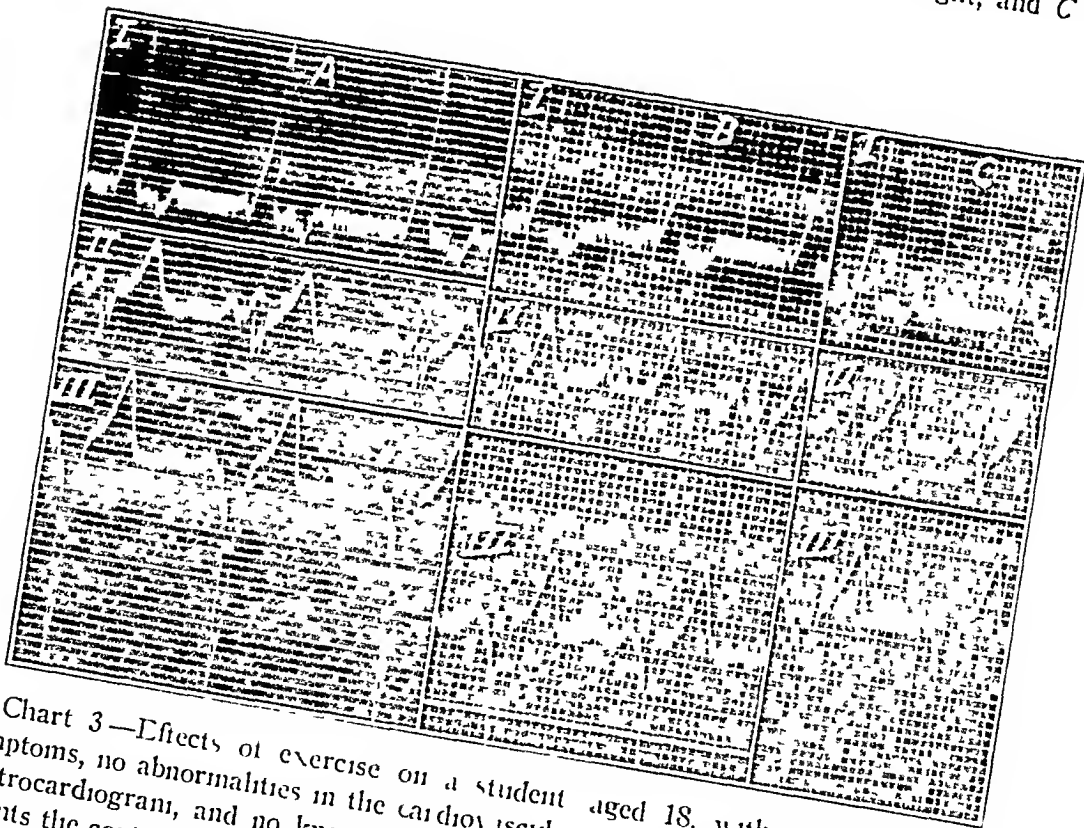


Chart 3—Effects of exercise on a student aged 18, with no cardiovascular symptoms, no abnormalities in the cardiovascular examination, except this striking electrocardiogram, and no known etiology of any cardiovascular disease. A represents the control tracing, B, after running up four flights of stairs, the T waves did not show any striking change, and C, five minutes later (identical with 1)

inverted T wave, a definite inversion of a flat T wave or a deviation of the S-T interval from the iso-electric line

With these observations as a background for comparison, we reexamined our angina pectoris tracings. It was found that fifteen of them showed no changes other than those that had been seen in our control group. However, the remaining fifteen showed definite, temporary alterations in the ventricular complexes during the pain, unlike any seen in the control series¹² (charts 5, 6, 7, 8, 9, 10, 11 and 12, cases 1 to 15)



Chart 4—Effects of exercise on a man, aged 43, with no demonstrable cardiovascular abnormalities. *A* represents the control tracing, *B*, tracing taken after running up eight flights of stairs, patient quite exhausted, T_1 reduced in size, parallel to the reduction in R_1 , other T waves increased in size, and *C*, tracing made five minutes later

Further analysis of our tracings, arbitrarily dividing the attacks into mild and severe ones, showed that of the fourteen patients with severe

¹² Judged on this basis, Bousfield's case, Levy's four cases, and one of Feil and Siegel's cases can be considered to show definite specific changes. Two more of Feil and Siegel's cases showed less definite specific changes, but can probably be included in this group



Chart 5—Tracing of patient no 2 (case 2) *A*, control tracing, *B*, during attack, T_2 became inverted, *C*, five minutes after disappearance of the pain, identical with *A*

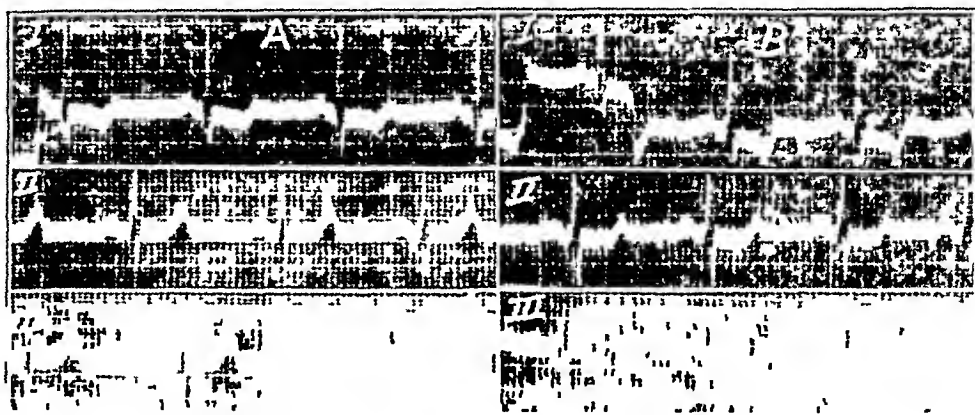


Chart 6—Tracing of patient no 3 (case 3) *A*, before attack, *B*, during attack, no tracing was taken after the pain had subsided. During the pain, T_1 became deeply inverted, T_2 became markedly reduced in height



Chart 7—Tracing for patient in case 4 *A* is the control tracing, *B*, one taken during an attack caused by walking up three flights of stairs, *C*, tracing taken five minutes later, and *D*, tracing taken four weeks later during an attack caused by walking up four flights of stairs. During the pain T_2 became diphasic and T_3 more deeply inverted, T_1 also showed minor changes, especially in *D*

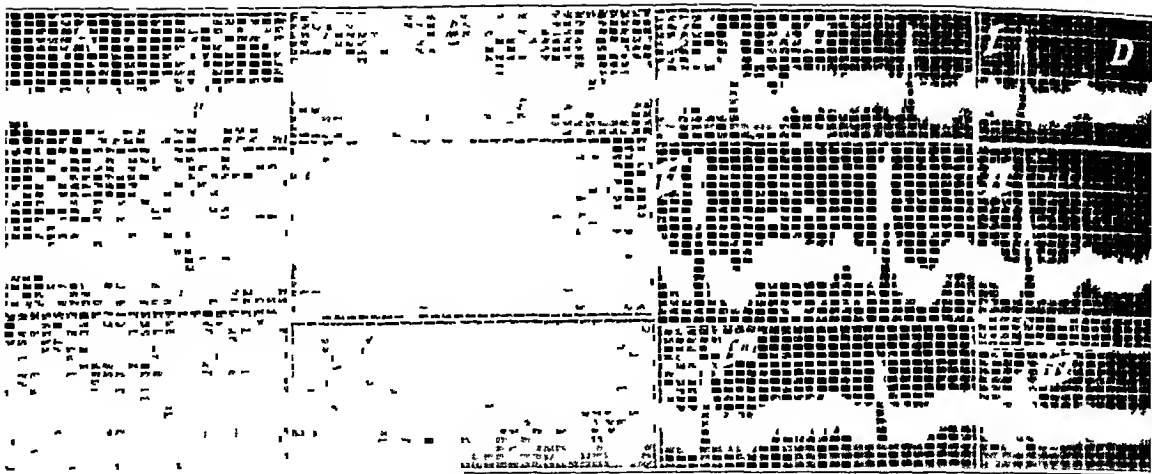


Chart 8—Tracing of patient no 6 (case 6) *A* is the control tracing, *B*, tracing made during attack of pain, S-T interval depressed in lead II, T_2 sharply inverted, and *C*, tracing made immediately after the disappearance of pain T_1 and T_2 were both quite deeply inverted *D*, the tracing made two minutes later, was similar to *A* The changes were somewhat more noticeable immediately after the pain subsided, although they were present during the pain

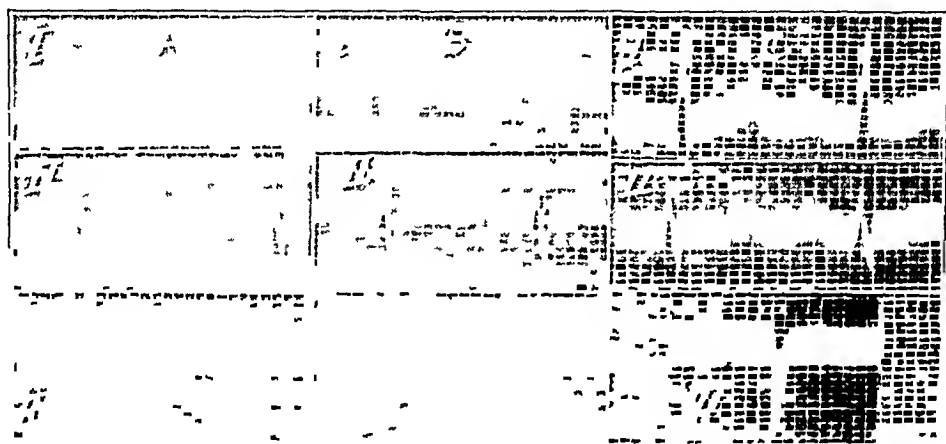


Chart 9—Tracing of patient no 9 (case 9) *A* is the control tracing, *B*, that taken during pain, the "specific" change in this tracing is the peculiar contour of T_2 during the attack, *C*, taken four minutes after the pain had disappeared

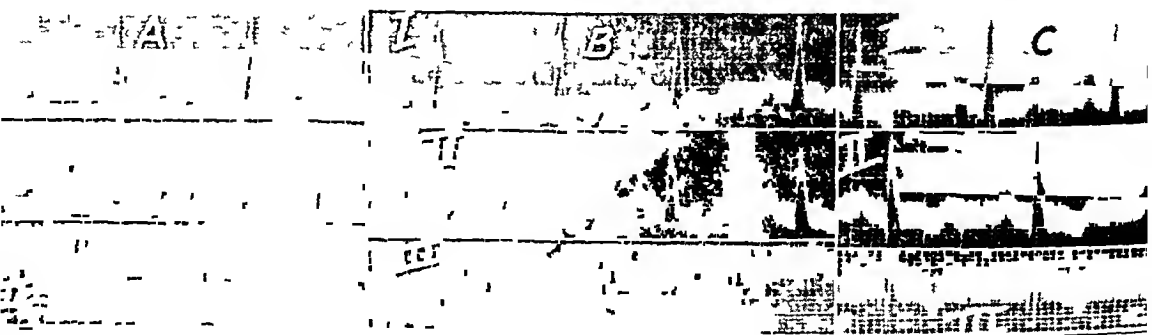


Chart 10—Tracing of patient in case 12 *A*, control tracing, *B*, tracing made during pain, T_1 became inverted and T_2 became more deeply inverted than it had been the T_2 changes are marked, but are in the "normal" direction, *C*, tracing made four minutes after pain had disappeared

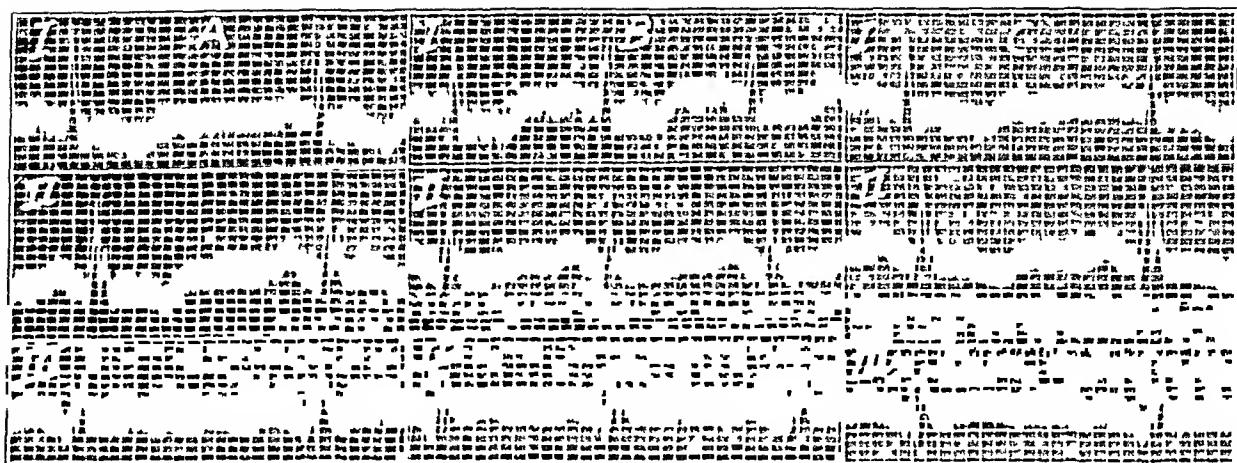


Chart 11—Tracing of patient in case 14 *A*, control, *B*, during pain, the S-T interval in lead I was definitely depressed *C* two minutes after the pain had disappeared, identical with *A*



Chart 12—Tracing of patient in case 15 *A* is the tracing taken during pain, *B*, that taken four minutes after the subsidence of pain, the S-T interval in leads II and III took on an abnormal contour during the pain, the "specific change in this case is less marked than in the other cases

attacks, seven showed specific change and seven did not. Of the sixteen patients with mild attacks, eight showed specific change and eight did not. The severity of the pain, therefore, did not appear to bear a definite relation to the presence or absence of electrocardiographic changes in different persons.

In the same subject the electrocardiographic phenomena accompanying each of several attacks were the same in character, whether the attack was spontaneous or induced. However, they varied somewhat in degree. The more severe and prolonged the attack, the more pronounced were the electrocardiographic changes.⁹

For obvious reasons attacks were not generally induced in patients with the severest types of angina, nor in those with electrocardiographic evidence of marked myocardial disease. This type of patient might be expected to show the most pronounced electrocardiographic change during the attack.¹³

In most of our cases the alterations in the ventricular complexes were most pronounced when the paroxysm was at its height, and disappeared within a minute or two after the pain subsided. In three cases (cases 6, 7 and 13, chart 8), the most pronounced changes appeared shortly after the pain had ceased.

Therefore it appeared that in 50 per cent of our cases, the pain of the anginal attack was associated with and generally paralleled by, a change in the ventricular complex of the electrocardiogram that could not be explained by the exercise which produced the attack nor by the changes in blood pressure and pulse rate which accompanied it. It seems reasonable to suspect, though it can certainly not be considered proved, that some specific intrinsic change takes place in the heart itself during the paroxysm which causes this change in the electrocardiogram.

EXPERIMENTS ON ANIMALS

The following group of observations deals with the possible nature of the cardiac change, the presence of which is suggested by the electrocardiographic study of attacks of angina pectoris. The question that we have attempted to answer is: Can the electrocardiographic and other phenomena of an anginal attack be explained on the basis of a temporary interference with the blood supply to a part of the heart muscle (i. e., by the coronary hypothesis)?

The Electrocardiographic Phenomena—We know from the work of F. M. Smith¹⁴ and others¹⁵ that ligation of a coronary artery in an

¹³ Bousfield (footnote 8, first reference)

¹⁴ Smith, F. M. The Ligation of Coronary Arteries with Electrocardiographic Studies, *Arch Int Med* **22** 8 (July) 1918

¹⁵ Kahn, R. H. Elektrokardiogrammstudien, *Pflüger's Arch f d ges Physiol* **140** 627 (June) 1911

experimental animal will produce a permanent change in the electrocardiogram. Similarly, in man a coronary occlusion may give rise to well recognized alterations in the ventricular complex.¹⁶ Otto¹⁷ recently published a brief report of the effect of temporary coronary occlusion on the electrocardiogram in animals. However, to our knowledge, no one has as yet performed a satisfactorily critical set of experiments to enable one to answer the following questions:

(a) Will temporary interruption of a part of the coronary circulation in the experimental animal produce temporary and rapidly reversible electrocardiographic changes analogous to those seen in our angina pectoris tracings?

(b) Will the heart recover and the electrocardiogram return to its previous state after the heart has suffered a disturbance of a part of its blood supply of sufficient magnitude and duration to produce electrocardiographic changes?

In order to answer these questions, we studied the effects of temporary coronary obstruction in a series of eight dogs and six cats.

TECHNIC

The chest was opened in the midline anteriorly, under iso-amyl-ethyl barbituric acid anesthesia and artificial respiration. The pericardium was opened and sutured loosely to the sides of the chest in order to make a hammock for the heart, which prevented any change in its position. Care was taken not to interfere with the flow of blood to or from the heart. Electrocardiographic electrodes were fastened to the two fore limbs and the left hind limb. In some of the experiments the carotid was cannulated for a blood pressure record. Electrocardiograms in three leads were taken before, during, and after temporary occlusion of the various coronary vessels. At times a continuous record was taken in lead II throughout the whole procedure.

The technic of occluding the vessels was varied. Usually it consisted in placing a bulldog clamp on the undissected artery and periarterial structures, sometimes including the accompanying vein. Frequently the various arteries were dissected free from surrounding structures and occluded by means of clamps or ligatures. When a ligature was used, a small glass rod was included in the knot to facilitate its release.

The results of clamping a large coronary artery become apparent in fifteen seconds. The cardiac contraction changes character in a manner that defies description, and a definite cyanosis of the myocardium appears strictly limited to the area supplied by the occluded vessel. This cyanosis is not dependent on venous obstruction. After a minute or two, the involved ventricle begins to dilate, and if the clamp

16 Levine, S. A. Coronary Thrombosis. Its Various Clinical Features, *Medicine* 8:245 (Sept.) 1929.

17 Otto, H. L. The Effect of Obstruction of the Coronary Arteries upon the T-Wave of the Electrocardiogram. *Am. Heart J.* 4:347 (Feb.) 1929.

is not soon removed the ventricles may begin to fibrillate. However, if the clamp is removed before fibrillation commences, the heart may recover its original appearance, provided the vessel has not become permanently occluded. The time necessary for recovery is proportional to the duration of the occlusion. It also varies with the original state of the heart, i. e., whether it is fresh or whether it has been used in previous similar experiments.

The electrocardiographic phenomena produced by interruption of certain parts of the coronary circulation are striking. The types of ventricular complex alterations observed and the time intervals involved in their appearance and disappearance are illustrated in the charts 13 to 16. Certain factors seem to be important in the production of these electrocardiographic changes. (a) The vessel which is occluded. In general, more striking changes followed the clamping of the vessels on the posterior surface of the heart, i. e., the circumflex branch of the

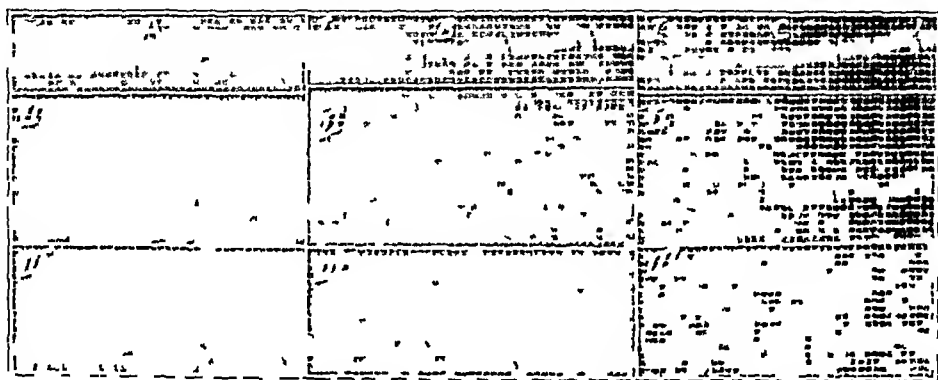


Chart 13—Tracing of a dog. *A*, the control tracing definitely abnormal, *B*, the tracing taken one minute after clamping the posterior descending coronary artery, with its accompanying vein, T_2 and T_3 became more deeply inverted, the clamp was removed immediately after *B* was taken, *C*, one minute after the removal of the clamp, identical with *A*.

left and the posterior descending coronary arteries. Usually little or no change was produced by obstruction of the right or of the anterior descending branch of the left coronary artery. (b) The size of the area of the myocardium the blood supply of which is interrupted. More marked changes followed the simultaneous obstruction of both main branches of the left coronary artery (the anterior descending and the circumflex) than followed the obstruction of either one separately. (c) The simultaneous obstruction of accompanying veins. This factor has not been accurately evaluated in our experiments. It may be of considerable importance. Nevertheless when the arteries were dissected out and occluded without venous obstruction, definite and striking changes were observed (chart 16). (d) The state of the heart before the occlusion. Coronary occlusion in a healthy fresh heart does not

produce electrocardiographic changes as readily as it does in a damaged one. In our experiments, the same heart was used repeatedly for successive coronary clampings, with suitable periods intervening for recovery. Rapidly reversible alterations in the ventricular complexes were much more readily obtained after myocardial damage, incident to previous manipulation, had produced a certain amount of permanent electrocardiographic change (charts 13 to 16). Our results toward the end of a period of experimentation on an animal were much more striking than our earlier ones. Bousfield's case¹³ showed that the most striking electrocardiographic changes possibly occur in man during attacks of angina pectoris when there is similar evidence of severe myocardial disease in the control tracing. (c) The duration of the occlusion. The longer the clamp was left in place, the more pronounced were the changes in the ventricular complexes (chart 15).

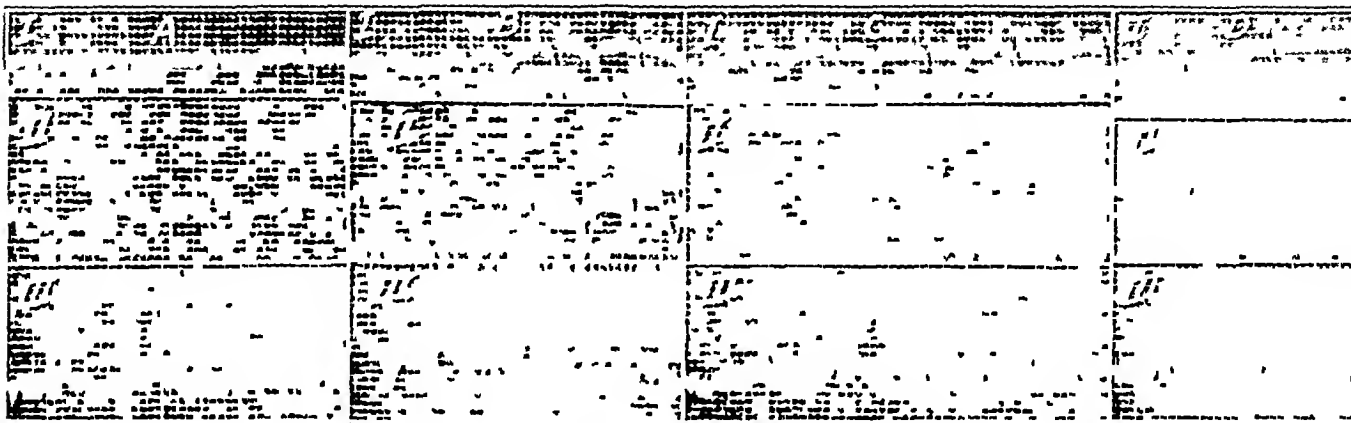


Chart 14—Tracing of a dog. *A*, control tracing, definitely abnormal, *B*, the tracing taken one minute after clamping of the posterior descending coronary artery, with its accompanying vein, increased inversion of all T waves, the clamp was removed immediately after *B* was taken, *C*, one minute after the removal of the clamp, *D*, one minute after *C*, identical with *A*.

More striking electrocardiographic phenomena resulted from coronary occlusion in dogs than in cats. Change in position of the heart was not a factor in these electrocardiographic changes. Dilatation of the heart was probably not responsible for them, since it often occurred without producing any marked alteration in the tracing.

It appears that (a) Temporary interference with the blood supply of a part of the heart muscle may produce temporary and rapidly reversible electrocardiographic changes analogous to those seen in our angina pectoris tracings. (b) These changes may appear and disappear within two minutes, a period of time comparable to that involved in an anginal attack. (c) The heart may recover and the electrocardiogram return to its previous state after the myocardium has suffered an ischemia of sufficient magnitude and duration to produce electrocardiographic changes.

(a) *Arrhythmia*—One of Sir Clifford Allbutt's reasons⁴ for discarding the coronary hypothesis and ascribing angina pectoris to an extracardiac cause was his belief that myocardial ischemia must of necessity produce arrhythmias (extrasystoles and ectopic rhythms arising from the ischemic area), which are notoriously missing from the clinical picture of angina pectoris. Our studies tend to invalidate this feature of Allbutt's hypothesis. In our experiments extrasystoles did not usually occur until late, just before the ventricles began to fibrillate¹⁸. Our observations are also in line with the clinical fact that when irregularities of the heart do occur during an anginal attack, they appear near the end of a prolonged paroxysm, and their appearance is of ominous prognostic significance.

(b) *Blood Pressure*—In all of our patients with angina pectoris except two (cases 14 and 22), there was a moderate rise of blood



Chart 15—Tracing of a dog. *A*, control tracing, abnormality of S-T interval, *B*, the tracing taken fifteen seconds after clamping the posterior descending coronary artery, with the accompanying vein, moderate change in ventricular complexes, *C*, one minute after *B*, clamp still in place, tracing shows typical R-T fusion of myocardial infarction, the clamp was then immediately removed, *D*, tracing taken three minutes after the removal of clamp there was considerable return toward contour of normal tracing, *E*, tracing taken seven minutes after *D*, identical with *A*.

pressure during the paroxysm. In our animal experiments an invariable immediate drop of blood pressure, varying in degree with the size of the vessel, was obtained whenever a large coronary artery was occluded. The objection raised against the coronary hypothesis by these observa-

¹⁸ Extrasystoles, which appeared occasionally at the time of application of the clamp, were attributed to incidental mechanical stimulation of the myocardium since a reduction of this mechanical stimulation to a minimum tended to prevent their appearance. We believe that a similar mechanism can account for extrasystoles, reported by other authors to have been caused by coronary occlusion. Sutton and King, *Proc Soc Exper Biol & Med* 25 842, 1928. Pearce, Priest, and Van Allen, *Am Heart J* 4 390, 1929.

tions is not insurmountable. The blood pressure phenomena appearing during an experiment on an anesthetized animal cannot be expected to be reproduced exactly in a conscious man. The pressor reflexes set up by the pain of an anginal attack seem adequate to counteract a moderate fall of blood pressure due to a temporary myocardial ischemia. This belief is supported by the case reported by Fitz,¹⁹ the only one which has come to our attention in which a patient has been observed during and immediately after a coronary occlusion. The clinical and electrocardiographic features make it relatively certain that a coronary occlusion did take place, nevertheless, the coronary accident was accompanied by a rise of blood pressure. The possibility presents itself that coronary occlusion produces an immediate rise of blood pressure in many cases, giving place to a subsequent fall at the time when these cases are usually seen by physicians. This explains the current belief

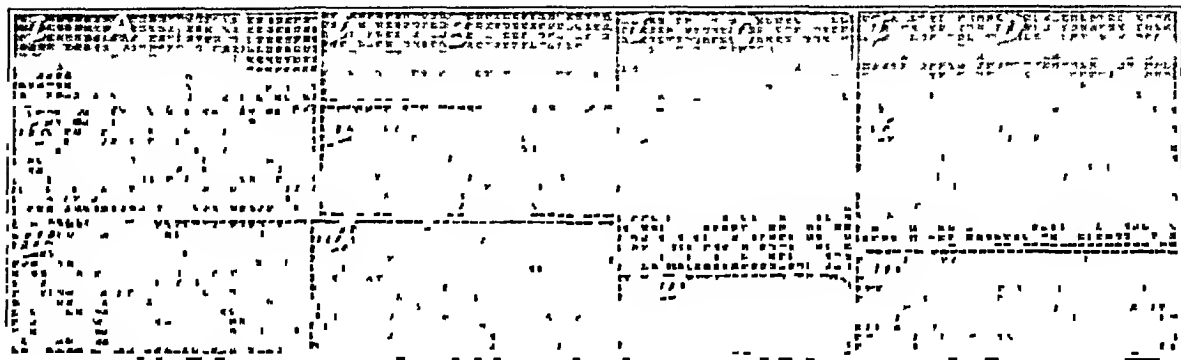


Chart 16—Tracing of a dog. *A* is the control tracing, showing considerable abnormality, *B*, that taken a half minute after clamping of both branches of the left coronary artery (anterior descending and circumflex), this tracing shows R-T fusion typical of myocardial infarction. In this instance the arteries had been dissected free, and there was no venous obstruction, the clamps were removed at once, *C*, the tracing taken one minute after the removal of clamp, the tracing shows considerable recovery, *D*, that taken two minutes after *C*, and identical with *A*.

that coronary occlusion and a drop in blood pressure are inseparable phenomena.

(*c*) *Pain*—References to the work of Singer, Sutton and King and of Percy, Priest and Van Allen³ make it more than probable that there are nerves in the adventitia of the coronary arteries that can produce pain when suitably stimulated. We do not wish to speculate too far on the mechanism of pain production in angina pectoris, but it seems possible that a sudden change in the chemical nature of the blood bathing these nerves might be a sufficient stimulus to give rise to pain.

¹⁹ Fitz, Reginald. A Case of Angina Pectoris with Cardiac Infarct Induced by the Intravenous Injection of Sodium Tetra-Iodophenolphthalein, and Followed by Relief of Anginal Symptoms, *Tr. A. Am. Phys.* **43** 292, 1928.

Moreover, a chronic anoxemia of these nerves, such as would be present in congestive failure, might decrease their irritability sufficiently to explain the well known dictum "When heart failure supervenes, angina pectoris disappears." Mackenzie's explanation²⁰ that heart failure stops the patient before he can exert himself sufficiently to produce an attack of angina has not seemed to explain some of our observations.⁷ Another possible explanation of the relief of angina by congestive failure is suggested by the recent work of Bellet and Batson²¹ concerning the reversal of blood flow in the coronary veins under certain conditions.

A few other noteworthy facts presented themselves during the course of our work.

1 Sometimes the experimental occlusion of a large coronary artery, with the consequent production of a definite change in the appearance and action of the heart, caused no change in the electrocardiogram. This has a definite bearing on those fifteen patients whose tracings showed no specific change during attacks of angina pectoris. It shows that the absence of electrocardiographic change during an attack of angina pectoris cannot be used as evidence that temporary myocardial ischemia did not occur. Therefore, although some mechanism other than the coronary one might be operating to produce the paroxysm in a case showing no specific ventricular complex change during a severe attack, it is possible for such a case to be due to myocardial ischemia.

2 Levine, Ernstene and Jacobson²² recently published an interesting group of electrocardiograms taken during attacks of precordial pain which were produced in patients with angina pectoris by injections of epinephrine. All the electrocardiograms reported in their paper show changes in the "normal" direction (i. e., the type seen in controls), differing from their controls in degree but not in direction of change. We have seen such changes (case 24) in several patients during attacks induced by exertion, but in our analysis we have not considered any changes "specific," although they may well have been, unless the alterations were in the opposite direction, or of an entirely different nature, from those seen in our control series. It may be that the epinephrine dilates the coronary vessels and thereby masks the true nature of the electrocardiographic changes due to angina pectoris in itself.

3 The electrocardiographic phenomena caused by inhalations of amyl nitrite are so diverse as to defy analysis at present. Nothing can

20 Mackenzie, Sir James. *Angina Pectoris*, Frowde, London, 1923.

21 Bellet, Samuel, and Batson, Oscar V. Personal communication. Unpublished experiments.

22 Levine, S. A., Ernstene, A. C., and Jacobson, B. M. The Use of Epinephrine as a Diagnostic Test for Angina Pectoris, *Arch Int Med* **45** 191 (Feb) 1930.

be said except that amyl nitrite can cause profound changes in the electrocardiogram. The blood pressure, which is frequently profoundly depressed within fifteen seconds after inhalation of amyl nitrite usually rebounds to a level of from 10 to 20 mm above its original one from fifteen to thirty seconds after the inhalation has been stopped. It seems unlikely therefore that relief from anginal pain by nitrites depends on the drop of pressure which they produce.²³ F. M. Smith's experiments²⁴ showing that nitrites will cause a visible reduction in the size of an ischemic area in the heart suggest a more satisfactory explanation. It is noteworthy in this connection that the two cases in our series in which there was a fall of blood pressure during the attack gave a history of definite relief by nitrites.²⁵ In one of them (case 22) inhalation of amyl nitrite was accompanied by a rise of blood pressure coincident with relief from pain.

4 The mechanism of death in angina pectoris has long been a matter of dispute. Allbutt¹ explained it as a vagal arrest of the heart. Wenckebach⁵ varied this explanation somewhat. Supporters of the coronary hypothesis attribute anginal death to ventricular fibrillation due to myocardial ischemia. In this connection, a case of Sir William Osler's⁶ has always interested us. This patient presumably died in an attack of angina pectoris, whereupon Osler inserted a needle through the chest wall into the heart and observed a slow regular impulse transmitted to it, not like that which might have been expected to arise from a fibrillating heart. No heart sounds were heard at the time. During our animal experimentation we frequently observed, as did Hooker,²⁶ that when the ventricles were fibrillating the auricles continued to beat rhythmically. It seems quite possible that the rhythmic impulse Osler observed was auricular in origin, and that this observation can be fitted into the coronary hypothesis.

5 It has long been known that there are in general, two types of angina with regard to the relation of exertion to the production of the attack. These two types more or less shade off into one another, and there is no definite line of demarcation between them. However, at the two extremes there is, first, the type that is quite regularly produced by a certain amount of increase in cardiac activity (exertion, excitement, etc.) and that subsides quite rapidly when this over-activity of the heart

23 Brunton L. *The Therapeutics of the Circulation*, Philadelphia, P. Blakiston's Son & Company, 1908.

24 Smith, F. M. The Action of Nitrites on the Coronary Circulation, *Arch Int Med* **28** 836 (Dec.) 1921.

25 One of these cases showed no electrocardiographic change during the attack (case 22), one showed specific change (case 14).

26 Hooker, D. R. On the Recovery of the Heart in Electric Shock, *Am J Physiol* **91** 305 (Dec. 1) 1929.

ceases (i.e. at rest) Second, there is the type in which the attacks are paroxysmal, spaced far apart as a rule, and are not related to exertion but seem to come like a thunderbolt out of a clear sky This type usually lasts longer, is severe, and is not so definitely and immediately relieved by rest All of our cases except one belonged to the first group The case in the second group (case 15) showed a slight but definite change in the electrocardiogram during the attack, (chart 12) Nitrites relieved this patient's paroxysms, on a regimen of restricted activity and vasodilator medication he obtained complete freedom from attacks More cases of this type should be studied before deductions can be made as to the etiologic mechanism involved The case is specifically referred to at this time because electrocardiograms are not usually obtained in this type of patient during the attack

6 The use of our electrocardiographic procedure to diagnose angina pectoris is not recommended Although there were no untoward occurrences in our series of cases, it is admittedly dangerous to induce anginal attacks indiscriminately Moreover, 50 per cent of cases give no diagnostic electrocardiographic phenomena, and the significance of changes that may appear in the ventricular complex is still open to question In a doubtful case, with a relatively healthy cardiovascular apparatus, an attempt to induce an attack by moderate exercise may be permissible and may yield important information, but the clinical observations are more likely to be significant from a diagnostic standpoint than the electrocardiographic phenomena

7 We have attempted to determine whether any prognostic significance can be attached to the presence or absence of changes in the electrocardiogram during the attack of angina pectoris There are so many other factors involved in the prognosis⁷ that any attempt to predict the outlook of a patient by such a procedure alone would be ludicrous However, it is noteworthy that in this series all of the five patients who died showed specific electrocardiographic changes during their attacks A more prolonged observation of this group of patients is necessary before any significance can be attached to these observations

SUMMARY

Thirty cases of angina pectoris were studied electrocardiographically before, during and after their attacks Fifteen showed temporary ventricular complex changes during the pain, which probably cannot be explained by the exercise which produced the attacks nor by the changes in blood pressure and pulse rate which accompanied them

The remaining fifteen showed no "specific" electrocardiographic changes during their attacks

The severity of the pain did not seem to be the main factor that determined the presence or absence of "specific" electrocardiographic change during an attack

The relief of anginal pain by nitrites does not always seem to be dependent on the drop of blood pressure which this group of drugs produces

Although there were no untoward occurrences in our series of cases, we are not prepared at present to recommend the electrocardiographic procedure herein described as a diagnostic test in angina pectoris

The prognostic importance of "specific" electrocardiographic changes during attacks has not as yet been determined

In a series of dogs and cats, temporary interference with a part of the coronary circulation produced temporary and rapidly reversible changes in the electrocardiogram somewhat analogous to those seen during attacks of angina pectoris

The factors that seemed to be important in the production of these changes were (a) the vessel that was occluded, (b) the size of the area of the myocardium the blood supply of which was interrupted, (c) the state of the heart before the vascular occlusion, (d) the duration of the occlusion and (e) possibly the simultaneous obstruction of accompanying veins

Experimental temporary coronary occlusion frequently produced no electrocardiographic change. Therefore the absence of "specific" electrocardiographic change in fifteen patients during attacks of angina pectoris cannot be used as evidence that temporary myocardial ischemia did not occur

In experimental coronary occlusion, cardiac arrhythmia, which could be attributed to the circulatory disturbance in itself, was not a frequent early phenomenon. When it did occur, it seemed to be attributable to mechanical stimulation of the heart muscle by the mechanism producing the occlusion

The evidence presented is in accord with the hypothesis that the majority of attacks of angina pectoris are associated with a localized circulatory disturbance in the heart. It does not rule out the possibility that other mechanisms may produce paroxysms of precordial or substernal pain

CASES SHOWING SEVERE ATTACKS WITH "SPECIFIC" ELECTRO-CARDIOGRAPHIC CHANGE

CASE 1—Sw Fr, a man, aged 67, gave a history of onset of anginal attacks in February, 1926. The paroxysms were caused by exertion and relieved by nitrites. The blood pressure was 180 systolic and 80 diastolic. The pulse rate was 80. There was enlargement of the heart to the left, systolic murmurs were audible at the apex and base. The Wassermann reaction of the blood was negative. The patient died on Nov 16, 1928.

On April 16, 1928, a typical attack of ten minutes' duration was produced by the ascent of two flights of stairs. The pain was severe, it was located beneath the upper part of the sternum, radiating to the left scapula and down both arms to the elbows. The electrocardiogram taken before the attack showed left axis deviation, T_1 and T_2 inverted, T_3 flat. During the attack, T_1 became more deeply inverted, T_2 became upright and T_3 markedly upright. The T_1 change was the only definitely "specific" one. No tracing was taken after the attack had subsided.

CASE 2—F V C, a man, aged 67, gave a history of anginal attacks that began in November, 1928. The paroxysms were caused by exertion and relieved by nitrites. The blood pressure was 120 systolic and 60 diastolic. The heart was slightly enlarged to the left, there was a soft systolic murmur at the apex. In March, 1930, when the patient was last heard from, he was considerably worse.

On Sept 10, 1929, a typical attack of four minutes' duration was produced by slowly and carefully stooping to the floor ten times. The pain was severe, located at the apex, with no radiation. Chart 5 shows the electrocardiographic tracings in this case.

CASE 3—C E, a man, aged 65, had his first attack of angina pectoris ten days before his visit to our laboratory. The paroxysms were usually caused by exertion. Nitrites were not given. Three days after consulting us, he died in an attack.

On Dec 1, 1928, while the patient was at rest in the electrocardiographic room, shortly after the first tracing had been taken, an attack occurred spontaneously. The pain was severe, lasting fifteen minutes. It was located beneath the upper third of the sternum, there was no radiation. Chart 6 shows the electrocardiographic tracings in this case.

CASE 4—S S, a woman, aged 40, had been suffering from attacks of angina pectoris for a year. Her pain was caused by exertion and relieved by nitroglycerin. (The inhalation of amyl nitrite produced a preliminary exaggeration of the pain of an attack, but relieved it subsequently.) The blood pressure was 105 systolic and 70 diastolic. The heart was not enlarged. There were no murmurs. The Wassermann reaction of the blood was negative. When the patient was last seen on April 22, 1930, her condition was unchanged.

On April 15, 1929, an attack of angina pectoris of ten minutes' duration was produced by the ascent of three flights of stairs. The pain was severe. It began in the second left interspace 6 cm from the sternum, and radiated to the upper third of the sternum, to the third dorsal spine and down the left arm to the wrist. Chart 7 shows the electrocardiographic tracings in this case. (The patient was studied in a similar attack a month later.)

CASE 5—M G, a woman, aged 55, had suffered from attacks of angina pectoris since January, 1929. Her paroxysms were usually caused by exertion and relieved by nitrites. The blood pressure was 130 systolic and 40 diastolic. The pulse rate was 80. There was considerable enlargement of the heart to the left, with signs of marked aortic insufficiency. The Wassermann reaction of the blood was strongly positive. The patient died in October, 1929.

On July 7, 1929, the patient experienced a spontaneous attack of angina pectoris of ten minutes' duration while she was at rest in the electrocardiographic laboratory. The pain was severe, and accompanied by some dyspnea, it was located in the second and third left interspaces, and beneath the upper third of the sternum. During the attack the blood pressure rose to 160 systolic and 65 diastolic. When

the patient was free from pain, the electrocardiogram showed T_1 , 2 mm, T_2 , 0.5 mm, T_3 , -2 mm, it was normal in other respects. During the pain the S-T interval in lead I became slightly depressed, T_2 became flat, and the S-T interval in lead III became convexly curved upward. The same phenomena appeared during an attack which was induced at a subsequent date.

CASE 6—E A, a man, aged 38, first began to have attacks of angina pectoris three years previously. The paroxysms were caused by exertion. The administration of nitrites gave no relief. The blood pressure was 110 systolic and 70 diastolic. There was slight cardiac enlargement to the left, the aorta was slightly dilated and increased in density. No murmurs were audible. The Wassermann reaction of the blood was negative.

On March 14, 1930, a typical attack of angina pectoris was produced by stepping up on a chair fifty times. The pain was severe, lasting for four minutes, it was located in the xiphoid region, and did not radiate. During the attack the blood pressure rose to 188 systolic and 90 diastolic. Chart 8 shows the electrocardiographic tracings in this case.

CASE 7—R S, a woman aged 59, began to have attacks of angina pectoris two years previously. The pain was produced by exertion. Nitrites gave no relief. The blood pressure was 170 systolic and 90 diastolic. There was moderate enlargement of the heart in the region of the left ventricle. There were no murmurs, but the second sound at the aortic area was accentuated. The Wassermann reaction of the blood was negative.

On April 1, 1930, a typical anginal paroxysm of four minutes' duration was produced by walking slowly up six flights of stairs. The pain was severe, it was located in the second and third left interspaces, with no radiation. During the attack of pain the blood pressure rose to 208 systolic and 90 diastolic. The electrocardiogram taken before the attack showed a tendency toward left axis deviation, T_1 , 2.5 mm, T , 0.5 mm, T , -1.5 mm. During the attack T_1 reduced in height to 1.5 mm, T_2 became diphasic, - T remained -1.5 mm. The S-T interval became depressed in all three leads, particularly in lead II. In this case the most marked "specific" change appeared thirty seconds after the pain had subsided.

CASES SHOWING MODERATE AND MILD ATTACKS WITH "SPECIFIC" ELECTROCARDIOGRAPHIC CHANGE

CASE 8—M T, a man, aged 55, suffered from attacks of angina pectoris which were produced by exertion and relieved by nitrites. The blood pressure was 175 systolic and 100 diastolic. The heart showed moderate enlargement in the region of the left ventricle. The patient died Nov. 18, 1929.

On Jan. 10, 1929, a moderately severe paroxysm of pain of four minutes' duration was produced by mild exercise. The pain was located beneath the upper third of the sternum. The electrocardiogram taken before the attack showed T_1 , flat, T_2 , -3 mm, and T_3 , -2 mm. During the paroxysm T_1 became -2 mm, T_2 remained -3 mm with the S-T interval depressed, and T_3 became 1 mm.

CASE 9—H L, a man, aged 43, suffered from attacks of angina pectoris produced by exertion. The blood pressure was 130 systolic and 80 diastolic. There was no cardiac enlargement. The outcome in this case is unknown.

On Aug. 9, 1929, an attack of angina pectoris was produced by running up five flights of stairs. The pain, of moderate intensity, was located beneath the upper third of the sternum, and did not radiate. Chart 9 shows the electrocardiographic tracings in this case.

CASE 10—B H, a man, aged 42, suffered from attacks of effort angina. The administration of nitrites gave only slight relief. The blood pressure was 130 systolic and 85 diastolic. There was no cardiac enlargement, the aortic arch was slightly widened, there were no murmurs. When last heard from, on March 15, 1930, the patient was much worse, his attacks were more easily provoked and more severe.

On Oct 21, 1929, an attack of angina pectoris of two minutes' duration was induced by stepping up on a chair thirty times. The pain was located in the xiphoid region and was relatively mild in intensity. The electrocardiogram taken before the attack showed T_1 , 1.5 mm, T_2 , 2 mm, T_3 , flat. During the attack, the S-T interval in leads I and II showed a depression of 1.5 mm below the iso-electric line.

CASE 11—C A, a man, aged 48, gave a history of the onset of attacks of angina pectoris one month before consulting us. The paroxysms were produced by exertion, and considerably alleviated by nitrites. The blood pressure was variable, on one occasion it was recorded as 135 systolic and 70 diastolic, on another, 200 systolic and 180 diastolic. The heart was slightly enlarged to the left. The patient died in November, 1929.

On Nov 19, 1928, the patient was studied in two attacks. The first arose spontaneously, the second was induced by stepping up on a chair twelve times. In both attacks the pain was mild, it was located to the left of the sternum, in a band extending from the second to the fifth interspaces, with slight radiation to the left arm. During the pain the blood pressure was 175 systolic and 110 diastolic, after the attack had subsided it was recorded as 150 systolic and 100 diastolic. The electrocardiographic tracings taken when the patient was free from pain showed a left axis deviation. T_1 , 2 mm, T_2 , 2 mm, T_3 , 1.5 mm. The S-T interval in lead II was depressed 1 mm. During the pain the S-T interval in lead I became slightly depressed, in lead II it was depressed 2 mm, T_1 became slightly diphasic, and T_3 became 3 mm.

CASE 12—S Fr, a man, aged 38, had been suffering with mild attacks of angina pectoris for one month. The pain was produced by exertion, nitrites were not used. The blood pressure was 110 systolic and 64 diastolic. The heart showed moderate generalized enlargement. There were no murmurs. The Wassermann reaction of the blood was negative. When the patient was last heard from on April 1, 1930, the attacks had disappeared but he had restricted his activity considerably.

On April 10, 1929, an attack of moderate intensity was produced by the rapid ascent of ten flights of stairs. The pain was located at the cardiac apex and in the epigastrium. During the attack the blood pressure rose to 140 systolic and 80 diastolic. Chart 10 shows the electrocardiographic tracings in this case.

CASE 13—W D R, a man, aged 50, began to have attacks of angina pectoris three years previously. The paroxysms were produced by exertion. Nitrites were not used. The blood pressure was 140 systolic and 95 diastolic. There was no detectable cardiac enlargement, nor aortic dilatation. There were no murmurs, the aortic second sound was accentuated, however. When the patient was last heard from, on Feb 17, 1930, there had been no change in his condition.

On Dec 16, 1929, a brief but definite sense of substernal constriction, which lasted forty-five seconds, was produced by stooping to the floor forty times. During the episode, the blood pressure was 145 systolic and 80 diastolic. The electrocardiogram, taken before the attack showed T_1 , flat, T_2 , flat, T_3 , 0.5 mm,

and left axis deviation. During the attack T_1 became 1.5 mm and T_2 , 5 mm with the ST interval depressed 1 mm, and T_u , 2 mm. Immediately after the attack T_1 and T_2 became diphasic, and T_u became sharply inverted, —3 mm.

CASE 14—J. A., a man, aged 54, had suffered with paroxysms of angina pectoris for eighteen months. They were usually produced by exertion, but some attacks occurred during rest. The blood pressure was 150 systolic and 100 diastolic. The cardiac contour and size were normal. Systolic murmurs were audible at the apex and base. The outcome of this case has not been determined.

On April 29, 1930, an attack of pain of moderate intensity and of four minutes' duration was produced by stepping up on a chair sixteen times. The pain was located beneath the midsternum and did not radiate. During the paroxysm the blood pressure fell to 140 systolic and 100 diastolic, and continued to fall to 125 systolic and 100 diastolic, ten minutes after the attack. Chart 11 shows the electrocardiographic tracings of this case.

CASE 15—S. H., a man, aged 58, had suffered with paroxysms of angina pectoris for nine years. The attacks were not definitely related to exertion, but they came on without warning, were very severe, and lasted from twenty to forty-five minutes. Nitrites gave relief. The blood pressure was variable, being recorded as 133 systolic and 70 diastolic at one time, and 165 systolic and 105 diastolic at another. There was no cardiac enlargement. A systolic murmur was heard at the apex. When last heard from, March 20, 1930, the patient was completely free from attacks, living a life of moderately restricted activity.

On May 23, 1929, while the patient was sitting quietly in bed in the ward, a severe attack of pain developed. It was located beneath the entire length of the sternum, but was most severe beneath the lower part. The duration of the attack was twenty minutes. During the paroxysm the blood pressure was 155 systolic and 90 diastolic. After the pain subsided, it was 138 systolic and 70 diastolic. Chart 12 shows the electrocardiograms of this case.

CASES SHOWING SEVERE ATTACKS WITH NO "SPECIFIC" ELECTROCARDIOGRAPHIC CHANGE

CASE 16—C. B., a man, aged 47, gave a history of onset of anginal attacks on Jan. 1, 1929. The pain was caused by exertion, but not relieved by nitrites. The blood pressure was 130 systolic and 80 diastolic. The pulse rate was 110. There was slight enlargement of the heart to the left, and considerable aortic dilatation. No murmurs were audible. The Wassermann reaction of the blood was negative. When the patient was last heard from in March, 1930, there was no change in his condition.

On April 26, 1929, the patient walked into the electrocardiographic laboratory in an attack of pain caused by walking one square. The pain was located in the second left interspace, 5 cm. from the sternum, and radiated to the sternum, to the epigastrium and to the left shoulder and the scapula. The pain was severe and continuous for twenty minutes, it then gradually lessened, but did not entirely disappear for an hour. During the paroxysm the blood pressure was recorded as 145 systolic and 95 diastolic. The electrocardiogram taken during the anginal attack showed fairly small Q-R-S complexes, a tendency to left axis deviation. T_1 , 2 mm, T_2 , 3 mm, and T_3 , 0.5 mm, with a cardiac rate of 140. After the attack there was practically no change in the tracing except a reduction of rate to 110.

CASE 17—E. H., a man, aged 61, suffered with attacks of angina pectoris produced by exertion or excitement. The blood pressure in the right arm was 140

systolic and 90 diastolic, in the left arm, 95 systolic and 70 diastolic. The pulse rate was 95. There was no definite cardiac enlargement, but the aorta was markedly dilated. No murmurs were heard. The results of the Wassermann test of the blood were not reported to us.

In November, 1928, the patient was studied in an attack produced by walking up seven flights of stairs. The pain was severe, and lasted for eight minutes. It began near the left nipple, radiated to the midsternal region, down to the epigastrium, out to the left shoulder and down to the middle of the forearm. The electrocardiogram taken before the attack showed a tendency to low Q-R-S complexes, (highest 5 mm), T_1 , 2.5 mm, T_2 , 2 mm, T_3 , flat. During the pain, the tracing showed T_1 , 2.5 mm, T_2 , 3 mm, T_3 , -0.5 mm. (This slight inversion in lead III was not considered marked enough to constitute a definitely "specific" change.)

CASE 18—J F, a man, aged 50, gave a history of the onset of attacks of angina pectoris two months previously. The paroxysms were produced by exertion, they were not relieved by nitrites. The blood pressure was 125 systolic and 80 diastolic. When last heard from in March, 1930, he was considerably improved.

On July 25, 1929, a typical attack of angina pectoris was produced by walking up three flights of stairs. The pain was severe and lasted for five minutes, it was located beneath the middle third of the sternum, with no radiation. During the paroxysm the blood pressure rose to 160 systolic and 100 diastolic. The electrocardiogram taken before the attack was entirely normal, T_1 , 2.5 mm, T_2 , 2.5 mm, T_3 , flat. During the pain the tracing showed T_1 , 2.5 mm, T_2 , 3 mm, T_3 , flat.

CASE 19—E C, a woman, aged 53, had suffered with attacks of angina pectoris for two years. They were produced by exertion, and relieved by nitrites. The blood pressure was 200 systolic and 80 diastolic. There was moderate enlargement of the heart in the region of the left ventricle, the aorta was slightly dilated. No murmurs were audible, but the aortic second sound was accentuated. The Wassermann reaction of the blood was negative. When last heard from in April 1930, the patient was considerably worse.

On Nov 25, 1929, a typical attack of angina pectoris of five minutes' duration was produced by walking up two flights of stairs. There was severe pain near the apex of the heart, radiating upward, and to the midsternal region. The electrocardiogram taken before the attack showed marked slurring of the Q-R-S complexes, with a duration of 0.11 seconds, T_1 , 0.5 mm, T_2 , 1.5 mm, T_3 , flat. During the attack, R_1 diminished in height and R_3 increased in height, but there was no change whatsoever in the T waves. Frequent ventricular extrasystoles appeared during the pain, and lasted for some time after the pain had subsided.

CASE 20—W M B, a man, aged 40, began to have attacks of angina pectoris six weeks previously. The pain was produced by exercise. The blood pressure was 145 systolic and 90 diastolic. The heart was not enlarged. There were adhesions between the pericardium and diaphragm near the cardiac apex. When last heard from on Feb 28, 1930, the patient was much improved.

In January, 1930, an attack of angina pectoris was produced by four minutes of strenuous setting-up exercises. The pain was moderately severe and lasted for four minutes, it was located in the xiphoid region, and in the ulnar side of each forearm, but was more marked on the left. The blood pressure during the attack was recorded as 165 systolic and 100 diastolic. The electrocardiogram taken before the paroxysm showed T_1 , 1 mm, T_2 , 1 mm, T_3 , -1 mm. During the pain the tracing showed T_1 , 0.5 mm, T_2 , 1 mm, T_3 , 0.5 mm.

CASE 21—G K, a man, aged 43, had a history of attacks of effort angina, not definitely influenced by the administration of nitrites. The blood pressure was 170 systolic and 110 diastolic. There was considerable cardiac enlargement. The patient has not been heard from since this examination.

On Sept 5, 1929, an attack of angina pectoris was produced by walking up two flights of stairs. The pain was quite severe, being located in the region of the apex of the heart, and radiating across the lower part of the chest. During the attack the blood pressure was 190 systolic and 110 diastolic, some alternation of strength was noted in the various beats. The electrocardiogram taken before the attack showed marked left axis deviation, T_1 , diphasic, T_2 , 1 mm, T_3 , 1.5 mm. During the pain the tracing showed T_1 , slightly diphasic, with a height of 1.5 mm, T_2 , 1.5 mm, and T_3 , 1.5 mm.

CASE 22—J I, a man, aged 67, gave a history of onset of attacks of angina pectoris on April 18, 1929. The pain was produced by exertion and relieved by nitrites. The blood pressure was 105 systolic and 80 diastolic. The heart was not enlarged, the aorta was markedly sclerotic, no murmurs were heard. On April 15, 1930, when last heard from, the patient was improved.

On March 10, 1930, an attack of angina pectoris was induced by walking around the room swinging the arms. The pain was severe, and lasted for four minutes. It began in the epigastrium, radiated up across the chest to both shoulders and down both arms to the elbows. It was more intense on the left. The blood pressure during the pain fell to 65 systolic and 50 diastolic, during the inhalation of amyl nitrite it rose to 70 systolic and 50 diastolic, later, after the attack had subsided, the blood pressure was recorded as 85 systolic and 70 diastolic. The electrocardiogram taken before the attack showed left axis deviation T_1 , 0.5 mm, T_2 , 2 mm, T_3 , 0.5 mm. During the pain it showed T_1 , 0.5 mm, T_2 , 2.5 mm, T_3 , 0.5 mm. The patient was subsequently studied in another attack caused by walking up two flights of stairs, and in this attack the observations were similar to those reported above.

CASES SHOWING MILD ATTACKS WITH NO 'SPECIFIC' ELECTRO-CARDIOGRAPHIC CHANGE

CASE 23—R C B, a man, aged 58, began to have attacks of angina pectoris three months before he consulted us. They were produced by exertion and relieved by nitrites. The blood pressure was 145 systolic and 100 diastolic. The heart was not enlarged, a soft systolic murmur was heard at the apex. In March, 1930, when last heard from, the patient was in about the same condition as when we saw him.

On July 20, 1928, a mild attack of pain, lasting for one minute, was produced near the left scapula by stepping up on a chair thirty times. The electrocardiogram taken before the attack showed T_1 , -1 mm, T_2 , 1.5 mm, T_3 , 3 mm. During the attack it showed T_1 , -0.5 mm, T_2 , 2 mm, T_3 , 2.5 mm.

CASE 24—M Z, a man, aged 45, with a history of attacks of effort angina, was studied in an attack in December, 1928. The pain, caused by walking up three flights of stairs, was of moderate intensity and was located under the sternum. An electrocardiogram taken before the attack showed T_1 , 4 mm, T_2 , 3 mm, T_3 , -2 mm. During the pain the tracing showed T_1 , 2 mm, T_2 , 4 mm, T_3 , 3 mm. (This change might almost be classed as "specific," in view of the pronounced alteration resulting from relatively mild exertion, but it is not entirely different in character from that seen in some control tracings.)

CASE 25—M N, a man, aged 69, began to have attacks of angina pectoris one year before we saw him. The paroxysms were caused by exertion and relieved by nitrites. The blood pressure was 180 systolic and 90 diastolic. The patient had a history of a long-standing moderate hypertension. There was slight enlargement of the heart in the region of the left ventricle and dilatation of the aortic arch. When last heard from, in March, 1930, the patient showed no change in his condition.

On Sept 9, 1929, an attack of mild pain of two minutes' duration was induced by walking up one flight of stairs. The pain was located in the second left inter-space, and did not radiate. During the attack the blood pressure was recorded as 200 systolic and 115 diastolic. The electrocardiogram taken before the attack showed T_1 , 2.5 mm, T_2 , -2.5 mm, T_3 , -3 mm. During the attack, it showed T_1 , 2 mm, T_2 , -1.5 mm, T_3 , -2.5 mm.

CASE 26—S W, a man, aged 49, had suffered from attacks of effort angina for three years. The blood pressure was 110 systolic and 65 diastolic, the heart was slightly enlarged to the left, there was a soft apical systolic murmur. The patient has not been heard from since the following study was made.

In October, 1929, an attack of angina pectoris of three minutes' duration was induced by the ascent of two flights of stairs. The pain was of moderate intensity, it was located beneath the sternum, and did not radiate. The electrocardiogram taken before the attack showed left axis deviation T_1 , 1 mm, T_2 , 3 mm, T_3 , 2 mm. During the attack T_1 was 0.5 mm, T_2 , 3.5 mm, T_3 , 3 mm.

CASE 27—M G, a woman, aged 56, began to have attacks of angina pectoris in January, 1929. The pain was produced by effort, the effect of nitrites was not determined. The blood pressure was 215 systolic and 115 diastolic. There was moderate cardiac enlargement in the region of the left ventricle, the aorta was dilated, and the aortic second sound accentuated. The Wassermann reaction of the blood was negative. When last seen, in March, 1930, the patient stated that she was free from attacks.

On July 12, 1929, an attack of angina pectoris was induced by stepping up on a chair eight times. The pain, which was of moderate intensity, was located beneath the upper third of the sternum, and lasted one minute. During the paroxysm the blood pressure was recorded as 255 systolic and 120 diastolic. The electrocardiogram taken before the attack showed left axis deviation T_1 , 1.5 mm, T_2 , 2 mm, T_3 , 0.5 mm. During the pain, the tracing showed T_1 , 1.5 mm, T_2 , 2 mm, T_3 , 0.5 mm.

CASE 28—T E S, a man, aged 49, with a history of angina pectoris, was studied in an attack in November, 1928. The pain was induced by the ascent of one flight of stairs, it was mild, located in the upper sternal region and lasted for two minutes.

An electrocardiogram taken before the pain showed T_1 , 1 mm, T_2 , 2 mm, T_3 , 0.5 mm. During the pain, the tracing showed T_1 , 1.5 mm, T_2 , 2 mm, T_3 , 0.5 mm. In March, 1929, the patient's condition was reported unchanged.

CASE 29—I S, a man, aged 70, reported that the onset of his anginal attacks had occurred five years before he consulted us. They were produced by effort and relieved by nitrites. The blood pressure was 210 systolic and 100 diastolic. The heart was not enlarged nor the aorta dilated, despite a long-standing hypertension. In March, 1929, the patient's condition was reported to us as much improved, the attacks of pain had practically ceased.

On Nov 28, 1929, the patient came into the electrocardiographic laboratory with a spontaneous attack of moderate substernal distress, which radiated to the left shoulder and arm, and which lasted for three minutes. The electrocardiogram taken when the patient was free from pain showed T_1 , 1.5 mm, T_2 , 2.5 mm, T_3 , 1 mm. During the attack, T_1 was 1.5 mm, T_2 , 2.5 mm, T_3 , 1 mm.

CASE 30—F J L, a man, aged 43, reported that the onset of his anginal attacks had occurred one month previously. They were produced by exertion or excitement, the effect of nitrites had not been determined. The blood pressure was 125 systolic and 70 diastolic. The heart was of normal size and shape. There were systolic murmurs at the apex and base. His condition was reported to us in April, 1930, as unchanged.

On Feb 26, 1930, an attack of angina pectoris was induced by the ascent of eight flights of stairs at a rapid walk. There was moderate substernal discomfort which lasted for one minute. The electrocardiogram taken before the attack showed T_1 , 1.5 mm, T_2 , 1 mm, T_3 , -0.5 mm. During the pain the tracing showed T_1 , 2 mm, T_2 , 3.5 mm, T_3 , 1 mm.

(In all cases, except those in which a statement to the contrary is made, electrocardiograms were taken after the attack had subsided and were identical with the control tracing taken before the pain began.)

BASAL METABOLIC RATE OF MEDICAL STUDENTS AND NURSES IN TRAINING AT CHARLESTON, S C *

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Studies on the basal metabolic rate in tropical and subtropical climates have been made by de Almeida,¹ Sundstroem,² Hafkesbring and Borgstrom,³ Tilt⁴ and others. The conclusion is rather general that metabolism is somewhat lower in warmer climates. Temperature is usually assumed to be the controlling factor, but McConnell and Yagloglou⁵ found that when men were placed in heated chambers, the change in basal metabolic rate was marked only when the increase in temperature and humidity was sufficient to break down the regulating mechanism of the body, then metabolism increased.

Lowered intake of protein has also been supposed to explain lower metabolism in the tropics, but Brooks⁶ showed that among college students dietary habits as to protein at New Orleans are not different from those at Cleveland or at Chapel Hill, N C.

Although the determination of the metabolic rate is most used clinically as an indication of the degree of activity of the thyroid, a gland the function of which is known to be affected by several factors other than climate, attempts to correlate or rule out differences in available iodine in the environment have not been made.

Conditions resulting from a lack of iodine in fetal life and during infancy, namely, enlargement of the thyroid, myxedema and cretinism, are known to bring about a lowering of the basal metabolic rate. According to Plummer,⁷ the diffuse colloid goiter is least guilty in this

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1 de Almeida, A O. *Le metabolisme de l'homme tropical*, J de physiol et de path gén **22** 12, 1922

2 Sundstroem, E S. *Univ California Publ Physiol*, 1926, vol 6

3 Hafkesbring, R, and Borgstrom, P. *Am J Physiol* **79** 221, 1926

4 Tilt, J. *J Biol Chem* **86** 635, 1930

5 McConnell, W J, and Yagloglou, C P. *Pub Health Rep* **39** 3075, 1924

6 Brooks, F P. *Am J Physiol* **89** 403, 1929

7 Plummer, quoted by Du Bois, E F. *Basal Metabolism*, Philadelphia, Lea & Febiger, 1927, p 288

respect bringing about a lowering of from 8 to 18 per cent. Nevertheless since this condition is much more common than either of the others it has been used as an index of the deficiency of iodine in the environment of the people in different areas. The widely quoted studies of Olesen⁸ on men drafted for military service in the United States showed that enlarged thyroids are least common in the southeastern part of the country. Systematic examinations of school children have been made in many places where goiter is known to be endemic and there are schools in some parts of the country where practically every child has an enlarged thyroid. Examinations usually have not been made in areas where goiter is not a problem although Hayne⁹ reported the results of the examination of 17 600 school children by county health officers in twenty counties of South Carolina.

TABLE 1—*Temperature and Relative Humidity at Charleston, S. C.*

Month	Temperature Means			Relative Humidity, per Cent		
	Maximum	Minimum	Monthly	8 a m	12:30 p m	5 p m
Number of Years	76	56	50	41	12	41
January	57.9	42.8	50.2	81	63	76
February	59.5	44.5	52.0	80	64	75
March	65.5	50.2	57.8	79	62	75
April	72.0	57.1	64.7	75	61	74
May	79.6	65.7	72.8	75	60	70
June	85.4	72.4	79.0	77	65	78
July	87.8	75.0	81.5	79	68	80
August	87.2	74.6	80.9	82	68	80
September	82.7	70.7	76.7	83	68	80
October	74.6	60.8	67.6	80	62	77
November	68.0	50.7	59.2	79	61	75
December	57	44.1	51.4	81	65	76
Year	72.1	59.0	65.1	79	64	77

Since it is not improbable that many persons in an area deficient in iodine can be affected to an extent that would not be detected on palpation of the gland and since practically all standards of metabolic rate have been developed in regions where goiter is more common than it is in South Carolina the present study was undertaken in the hope that it might add to knowledge of this subject. From this point of view the results are disappointing as they show values for both men and women around 10 per cent below those of the Russell Sage Institute or the Mayo Foundation¹⁰. They are however of sufficient interest to be presented.

Situated on the coast and in near proximity to the Gulf Stream Charleston has a mean annual temperature of 66.1 F and a mean rela-

⁸ Olesen Robert. Pub Health Rep 42:3180 1927

⁹ Hayne J. A. Am J Pub Health 19:1111 1929

¹⁰ Boothby W. M., and Sanford I. Thirteenth International Physiological Congress, Boston Aug 19-24 1929

tive humidity of 77 per cent. Meteorological data furnished by the U. S. Weather Bureau are given in table 1.

Our subjects were normal healthy young men and women. The nurses were required to undergo a physical examination before being accepted for training, and minor defects were remedied as soon as practicable after admission. The men were members of the second and third year classes in medicine. In all, ninety-three women and forty men were used.

Our apparatus was the Roth modification of the Benedict machine with Collins' kymograph. Alcohol checks on this apparatus yielded the following values: 98.5, 100.1, 98.9, 101.4, 99.7, with an average of 99.72 per cent of the theoretical amount of heat evolved. We adhered closely to the standard procedure as to the previous preparation and handling of our subjects. We were able to make three determinations on each subject on successive days, so that the total number of separate determinations reported is 388.

The data are presented in detail in tables 2 and 3 and summarized in table 4.

Tilt⁴ reported an average value of 33.4 calories per square meter of body surface per hour for a series of fifty-two students at the Florida College for Women, between the ages of 17 and 25. This corresponds to a deviation of -10.6 per cent from the Aub-Du Bois standard. Tilt expressed the opinion that this is evidence that people in the south have a lower metabolism than those living in the more severe climate of the north. Conklin,¹¹ however, in a study of the relationship of the menstrual cycle to the basal metabolic rate, made daily determinations on a series of ten young women at the University of Minnesota for a period of a month or more each. Her work was done between October and March at a place with a severe winter climate, and the average of all her determinations showed a deviation of -10.5 per cent from the standard (table 5). In contrast to this result, Gustafson and Benedict¹² found 35.9 calories per square meter of body surface per hour, corresponding to a deviation of -3 per cent, for a group of twenty students at Wellesley College. It hardly seems probable, then, that the low values which we obtained are climatic.

Since it was suggested that some of these low values might be due to malnutrition, we compared the weight of all our subjects and those of Tilt with the standard tables of the Life Extension Institute. Of the fifty-two subjects studied by Tilt, thirty-two were underweight and twenty overweight for their height and age, the average deviation being

11 Conklin, C., and McClendon, J. F. Basal Metabolic Rate in Relation to Menstrual Cycle, *Arch. Int. Med.* **45**: 125 (Jan.) 1930.

12 Gustafson, F. L., and Benedict, F. G. *Am. J. Physiol.* **86**: 43, 1928.

TABLE 2—*Basal Metabolism of Student Nurses*

Subject	Age	Height, Cm	Weight, Kg	Dates, 1929-1930	Calories per Sq Meter per Hour	Deviation from Aub Du Bois Standard, per Cent
42	22	160	45	October 4 5 7	33.5 33.1 34.5	-9.5 -10.5 -6.8
43	22	163	58	October 4 5 6	36.8 34.2 35.4	0 -7.5 -4.3
49	21	158	47	October 8 9 10	31.3 31.8 31.2	-15.4 -14.0 -15.7
51	21	160	68	October 9 10	34.0 31.2	-8.1 -13.0
54	20	158	53	October 11 12 14	29.9 25.8 29.7	-19.2 -30.3 -19.7
55	21	153	45	October 11 12 14	37.4 33.2 30.7	+1.0 -10.3 -17.3
60	21	170	56	October 15 16 17	31.6 32.9 31.8	-14.5 -11.1 -14.0
61	21	162	48	October 15 16 17	30.8 31.5 33.6	-16.7 -14.8 -9.2
69	20	155	49	October 22 23	29.9 31.6	-19.2 -14.6
70	21	159	59	October 21 22 23 25 26	37.4 35.9 31.9 34.2 35.4	+1.1 -3.0 -14.0 -10.0 -6.8
78	19	160	48	October 24	36.1	-5.0
83	24	176	54	October 24 25 26	34.9 34.0 33.5	-5.7 -8.1 -9.5
87	34	156	61	October 28 29 30	36.6 36.8 33.3	+0.2 +0.8 -8.8
88	19	161	52	October 28 29 30	35.6 35.9 37.5	-6.3 -5.5 -1.3
96	19	158	59	October 31 November 1 2	31.8 33.7 32.5	-15.2 -10.1 -13.3
100	21	160	52	November 1 2 3	32.7 31.9 31.3	-11.6 -13.8 -15.4
107	19	168	53	November 4 5 7	34.8 34.4 32.4	-7.2 -8.3 -13.6
108	21	156	49	November 4 5 7	33.4 35.8 36.1	-9.7 -3.2 -2.4
122	25	168	58	November 11 12 13	31.9 31.3 30.9	-13.8 -15.4 -16.5
123	21	163	56	November 11 12 13	37.1 36.4 34.5	+0.3 -1.6 -7.2
131	18	163	61	November 14 15 16	32.3 29.0 31.8	-15.0 -23.7 -16.3
132	21	164	49	November 14 15 16	37.8 38.3 36.5	+2.3 +3.4 -1.4
140	23	161	60	November 18 19 20	35.2 35.6 35.8	-4.9 -3.8 -3.2

TABLE 2—*Basal Metabolism of Student Nurses—Continued*

Subject	Age	Height, Cm	Weight, Kg	Dates, 1929-1930	Calories per Sq Meter per Hour	Deviation from Aub Du Bois Standard, per Cent
141	18	165	61	November 18	38.2	+ 1.9
				19	36.5	- 2.7
				20	38.6	+ 2.9
149	18	168	56	November 22	33.1	-12.9
				23	32.8	-13.9
				24	33.1	-12.9
150	20	151	58	November 22	32.8	-11.4
				23	33.3	-10.0
				24	36.8	- 0.4
158	20	164	46	November 25	37.3	+ 0.8
				26	38.2	+ 3.2
				27	35.9	- 3.1
164	19	161	51	November 28	40.7	+ 8.5
				29	36.3	- 3.2
				30	38.5	+ 2.6
166	22	170	61	November 29	35.4	- 4.3
				30	33.4	- 9.7
				December 1	33.8	- 8.7
173	22	164	75	December 2	34.0	- 8.1
				3	32.1	-13.3
				4	33.6	- 9.2
174	22	159	50	December 2	32.6	-12.0
				3	33.3	-10.0
				4	33.1	-10.5
183	31	156	47	December 5	35.9	- 1.6
				6	35.1	- 3.8
				7	34.7	- 5.0
184	32	157	75	December 5	38.6	+ 5.8
				6	34.2	- 6.3
				7	32.8	-10.2
192	24	170	55	December 9	32.8	-11.4
				10	29.8	-19.5
				11	30.8	-18.1
193	21	160	52	December 9	35.4	- 4.3
				10	34.4	- 7.0
				11	36.6	- 1.1
201	19	170	57	December 12	34.0	- 9.3
				13	35.0	- 6.7
				14	37.4	- 0.3
203	24	176	105	December 12	33.3	-10.0
				13	30.3	-18.1
				14	29.8	-19.4
210	20	158	58	December 16	35.9	- 4.3
				17	34.5	- 8.0
				18	34.1	- 9.1
211	28	168	62	December 16	35.5	- 4.0
				17	33.7	- 8.9
				18	37.5	+ 1.4
213	19	165	48	December 17	35.5	- 5.3
				18	36.7	- 2.1
				19	36.0	- 4.0
219	22	167	54	December 19	32.9	-11.1
				20	31.2	-15.7
				21	33.8	- 8.7
220	20	164	51	December 19	34.2	- 7.5
				20	32.6	-11.9
				21	36.3	- 1.9
225	25	157	48	December 22	35.4	- 4.3
				23	31.8	-14.0
				24	33.3	-10.0
226	19	170	63	December 22	29.2	-21.0
				23	29.9	-19.2
231	22	164	59	December 26	38.6	+ 4.3
				27	34.0	- 8.1
				28	32.1	-13.2
232	20	161	52	December 26	32.7	-11.6
				27	30.9	-16.5
				28	30.6	-17.3

TABLE 2—*Basal Metabolism of Student Nurses—Continued*

Subject	Age	Height, Cm	Weight, Kg	Dates, 1929-1930	Calories per Sq Meter per Hour	Deviation from Aub Du Bois Standard, per Cent
238	22	162	49	December 30	32.3	-12.7
				31	34.2	-7.6
239	20	163	48	December 30	34.6	-6.5
				31	32.3	-12.7
				January 1	34.5	-6.8
244	20	170	60	January 3	34.8	-7.0
				4	41.0	+13.2
				5	38.0	+2.7
245	19	163	65	January 3	36.7	-2.1
				4	39.5	+5.3
				5	36.4	-2.9
250	20	160	68	January 6	33.7	-8.9
				7	31.0	-16.2
				8	28.4	-23.2
251	20	155	74	January 6	34.6	-6.5
				7	34.8	-5.9
				8	34.4	-7.0
259	18	156	66	January 9	37.7	-0.8
				10	39.4	+3.7
				11	35.8	-5.8
260	18	164	72	January 9	52.2	+40.0
				10	37.9	0
				11	40.3	+5.9
268	20	165	52	January 13	32.4	-12.4
				14	28.9	-21.9
				15	28.9	-21.9
269	26	162	77	January 13	37.8	+2.2
				14	36.6	-1.0
				15	36.9	0
277	18	169	55	January 16	38.2	0
				17	34.9	-8.8
				18	35.5	-6.6
278	18	165	69	January 16	34.6	-9.0
				17	36.2	-4.8
				18	37.2	-2.1
287	26	160	49	January 20	37.7	+1.9
				21	37.8	+2.1
				22	37.0	0.0
289	22	175	102	January 20	35.3	-4.6
				21	35.2	-5.1
				22	37.2	+0.5
297	19	166	62	January 23	39.8	+6.0
				24	40.8	+8.8
				25	39.2	+4.5
298	19	162	62	January 23	32.8	-12.5
				24	31.4	-8.4
				25	33.7	-10.1
306	21	165	65	January 27	36.3	-1.9
				28	36.8	-0.5
				29	35.8	-3.3
307	21	158	50	January 27	37.3	+0.8
				28	42.0	+13.5
				29	33.6	-9.2
322	20	166	50	February 3	37.3	+0.8
				4	35.1	-5.1
				5	34.1	-7.8
323	20	159	49	February 3	29.5	-20.2
				4	31.5	-14.9
				5	29.5	-20.2
331	20	166	59	February 6	34.2	-7.6
				7	33.8	-8.7
				8	32.1	-13.3
				8	32.5	-12.2
332	22	158	71	February 6	40.5	+9.5
				7	39.8	+7.6
				8	37.7	+3.5
339	22	174	78	February 10	34.0	-8.1
				11	33.8	-8.8
				12	34.4	-7.0

TABLE 2—*Basal Metabolism of Student Nurses—Continued*

Subject	Age	Height, Cm	Weight, Kg	Dates, 1929-1930	Calories per Sq Meter per Hour	Deviation from Aub Du Bois Standard, per Cent
340	24	164	51	February 10	38.2	+ 3.5
				11	34.9	- 5.8
				12	34.6	- 6.5
349	20	160	53	February 13	35.4	- 4.3
				14	32.7	-11.6
				15	33.9	- 8.4
350	21	156	48	February 13	35.9	- 2.9
				14	32.7	-11.6
				15	35.2	- 4.9
357	24	162	55	February 17	38.7	+ 4.6
				19	38.0	+ 2.7
				20	36.9	- 0.3
358	19	164	55	February 17	35.5	- 5.3
				19	35.9	- 4.4
				20	37.3	- 0.5
366	21	166	66	January 24	36.5	- 1.4
				25	31.4	-15.1
				26	32.3	-12.8
367	23	157	46	January 24	38.7	+ 4.6
				25	38.8	+ 4.9
				26	38.3	+ 3.5
372	19	164	49	February 27	35.1	- 6.4
				28	35.1	- 6.4
				March 1	31.9	-14.9
373	19	164	52	February 27	35.0	- 8.0
				28	32.0	-15.9
				March 1	31.7	-19.2
383	27	163	64	March 3	31.1	-16.0
				4	29.8	-19.5
				5	30.6	-17.3
388	19	174	72	March 6	36.2	- 3.4
				7	35.5	- 5.3
				8	33.9	- 9.6
389	18	164	59	March 6	39.7	+ 4.4
				7	39.8	+ 4.7
				8	38.4	+ 1.1
394	20	157	57	March 10	35.0	- 6.7
				12	32.4	-13.6
395	20	161	39	March 10	30.8	-17.8
				11	32.0	-14.7
				12	33.9	- 9.7
400	19	158	56	March 17	31.4	-16.3
				18	30.2	-19.5
				19	30.6	-18.4
401	21	164	54	March 17	36.2	- 2.2
				18	36.4	- 1.6
				19	37.7	+ 1.9
406	19	166	60	March 21	33.8	- 9.9
				22	32.4	-13.6
				23	33.9	- 9.7
407	19	168	60	March 21	34.9	- 6.9
				22	35.9	- 4.3
				23	32.5	-13.4
412	18	152	55	March 24	37.2	- 2.1
				25	35.2	- 7.4
				26	39.3	+ 3.4
415	23	161	53	March 28	38.4	+ 3.7
				29	37.5	+ 1.2
				30	37.1	+ 0.3
422	19	164	58	March 31	37.8	+ 0.5
				April 1	38.0	+ 1.2
423	19	168	57	April 2	34.6	- 8.4
				April 1	32.5	-13.4
432	20	167	63	April 2	33.7	-10.1
				April 17	36.2	- 2.3
433	29	175	61	April 18	37.9	+ 2.4
				19	36.3	- 1.9
				April 17	33.0	-10.9
				18	32.6	-11.9
				19	32.7	-11.7

TABLE 3—*Basal Metabolism of Male Medical Students*

Subject	Age	Height, Cm	Weight, Kg	Dates, 1929-1930	Calories per Sq Meter per Hour	Deviation from Aub Du Bois Standard, per Cent
71	22	172	57	October 21	33 0	-16 4
				22	38 4	- 2 8
				23	35 2	-11 0
80	24	164	58	October 24	37 9	- 4 1
				25	35 5	-10 0
				26	37 1	- 6 0
92	26	177	64	October 29	34 6	-12 4
				30	36 3	- 8 1
				31	33 6	-15 0
101	20	181	67	November 1	39 9	+ 1 0
				2	37 2	- 6 0
				3	38 5	- 2 5
109	31	175	68	November 4	36 4	- 7 4
				5	33 6	-15 0
				7	32 7	-17 2
110	22	175	66	November 4	35 9	- 9 0
				5	36 4	- 7 8
				7	41 1	+ 4 0
119	27	175	72	November 8	31 7	-19 8
				9	30 8	-23 0
				10	35 4	-10 4
124	26	175	66	November 11	30 1	-23 8
				12	31 2	-21 0
				13	33 1	-16 2
133	21	171	68	November 14	39 2	- 0 9
				15	41 5	+ 5 1
				16	41 2	+ 4 4
142	24	173	57	November 18	40 6	+ 2 8
				19	38 7	- 2 0
				20	36 4	- 7 9
148	22	180	68	November 22	40 3	+ 2 0
				24	38 3	- 3 0
160	25	169	63	November 26	41 5	+ 5 6
				27	36 2	- 8 4
				28	41 9	+ 6 0
167	22	179	50	November 29	39 2	- 0 8
				30	39 0	- 1 8
175	21	176	68	December 1	37 2	- 5 8
				2	40 8	+ 3 3
182	21	165	56	December 4	37 6	- 4 8
				5	38 4	- 2 8
				6	38 4	- 2 8
185	24	184	78	December 5	38 4	- 2 8
				6	37 8	- 4 3
194	20	182	72	December 9	31 9	-19 3
				10	36 7	- 7 0
				11	39 5	0 0
216	24	178	75	December 18	36 7	- 7 1
				19	36 7	- 7 1
				20	38 0	- 3 8
254	22	178	72	January 7	35 9	- 9 1
				8	35 4	-10 4
				9	37 4	- 5 3
261	23	177	62	January 9	37 5	- 5 1
				10	45 2	+14 4
				11	41 1	+ 4 0
270	24	175	66	January 13	35 9	- 9 1
				14	32 9	-16 7
				15	32 8	-16 9
305	22	168	55	January 23	45 8	+16 0
				24	40 5	+ 2 5
				25	43 5	+10 1
317	26	171	70	January 31	35 7	- 9 6
				February 1	38 6	-15 0
318	25	178	61	January 31	37 9	- 4 0
				February 1	36 3	- 8 1
327	22	182	62	February 4	38 7	- 2 0
				5	34 2	-13 8
				6	40 0	+ 1 3

TABLE 3—*Basal Metabolism of Male Medical Students—Continued*

Subject	Age	Height, Cm	Weight, kg	Dates, 1929-1930	Calories per Sq Meter per Hour	Deviation from Aub Du Bois Standard, per Cent
341	21	172	59	February 10	45.6	+15.5
				11	41.9	+6.0
				12	36.2	-8.4
348	26	175	61	February 12	40.6	+2.9
				13	38.3	-3.0
				14	37.6	-4.8
365	23	171	56	January 20	36.8	-6.8
				March 4	36.3	-8.1
374	26	176	89	February 27	40.8	+3.3
				28	33.8	-14.4
				March 1	38.5	-2.5
375	21	179	64	February 27	38.1	-3.5
				28	41.3	+4.6
				March 5	34.0	-14.0
428	26	177	70	April 14	38.0	-3.8
				15	37.7	-4.6
				16	36.5	-5.1
429	29	187	68	April 4	32.6	-17.6
				5	34.2	-13.4
				6	31.7	-19.8
434	23	185	73	April 7	33.8	-14.5
				8	32.1	-18.7
				9	37.7	-4.4
435	24	186	65	April 7	33.0	-16.5
				8	35.0	-11.4
				9	31.3	-18.2
440	26	175	58	April 10	36.4	-8.0
				11	38.0	-3.8
				12	35.0	-11.2
441	24	180	60	April 10	39.5	0.0
				11	40.8	+3.3
				12	41.7	+5.6
446	24	177	63	April 14	35.4	-10.4
				15	36.3	-8.1
				16	35.0	-11.4
447	24	168	56	April 14	38.6	-2.3
				15	35.0	-11.5
				16	35.0	-11.5
462	29	181	66	April 22	34.2	-10.9
				23	35.5	-10.1
514	24	181	67	May 13	38.2	-3.4
				14	38.0	-3.8
				15	37.7	-4.7
				3	42.7	+8.1
				4	39.9	+1.0

TABLE 4—*Summarized Basal Metabolic Rate*

	Age	Number	Average All Values, Calories per Sq Meter per Hour	Average Lowest Values, Calories per Sq Meter per Hour	Deviation from Aub Du Bois Standard, per Cent	
					All Values	Lowest Values
Student nurses	18	9	36.9	35.0	-2.9	-7.9
	19-24	74	34.4	33.0	-7.0	-10.8
	25-29	7	34.0	33.2	-8.1	-10.3
	30-34	3	35.3	33.6	-3.3	-8.0
All		93			-6.6	-10.4
Male medical students	20-21	7	39.1	36.6	-0.1	-7.3
	22-24	26	37.4	35.9	-5.5	-9.1
	25-29	12	35.8	34.2	-9.4	-13.4
	31	1	34.2	32.7	-13.4	-17.2
All		40			-6.1	-10.1

—2.3 per cent Of ninety women included in our study, fifty-two were underweight and thirty-eight overweight, the average deviation being —0.8 per cent, of the medical students, thirty-three were below normal weight and seven above, with an average deviation of —7.2 per cent It is certain that any degree of malnutrition that would seriously affect the metabolic rate would be reflected in changes in weight markedly greater than these

TABLE 5—*Basal Metabolic Rate of Women at the University of Minnesota*
(Calculated from the Data of Conklin and McClendon)

Subject	Age	Heat Production, Calories per Sq Meter per Hour			Deviation from Aub Du Bois Standard		
		Maximum	Minimum	Average	Maximum	Minimum	Average
M G	20	38.5	32.1	33.8	+4.1	—13.3	—8.7
L G	23	34.9	30.0	32.4	—5.7	—18.9	—12.4
M S	35	38.8	30.9	35.1	+6.3	—15.4	—3.8
Eve S	22	42.7	29.1	35.5	—15.4	—21.4	—4.1
E T	20	35.0	27.8	30.6	—5.4	—24.9	—17.3
G W	20	35.3	30.5	32.4	—4.4	—17.6	—12.4
C C	22	35.8	27.8	31.8	—3.2	—24.9	—14.0
P O	22	33.1	27.7	30.4	—10.5	—25.1	—17.8
E S	21	41.5	33.0	37.2	+12.2	—10.8	+0.5
H R	23	35.6	30.2	32.3	—3.8	—18.4	—12.7
Average				33.1			—10.5

TABLE 6—*Metabolism of Women in Relation to Deviation from Standard Weight*

Number	Average Deviation from Standard Weight, per Cent	Deviation from Aub Du Bois Standard, per Cent	
		All Values	Lowest Values
22	—14.6 (—10 or more)	—8.1	—10.9
30	—5.7 (0 to —10)	—7.6	—10.3
25	+5.6 (+10 to 0)	—6.7	—10.2
13	+21.6 (more than +10)	—5.5	—9.7

Nevertheless, there seems to be a slight correlation between deviations from the standard weight and the standard metabolic rate (table 6)

SUMMARY

Determinations of basal metabolism on ninety-three student nurses and forty male medical students at Charleston, S. C., showed results averaging about 10 per cent lower than the Aub-Du Bois standard. The results were compared with those of similar work done at Tallahassee, Fla., and Minneapolis. Climate, the relative amount of iodine in human environment, dietary habits, and the state of nutrition are not considered responsible for the low values obtained.

THE HEART RATE IN PROGRESSIVE MUSCULAR DYSTROPHY

STUDIES WITH THE CARDIOTACHOMETER¹

ERNST P BOAS, MD

AND

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NEW YORK

In view of the reports of Globus¹ and others on the presence of definite myocardial lesions in patients with progressive muscular dystrophy, it seemed of interest to study some phases of the functional integrity of the circulation in a group of such patients. Accordingly, we studied the heart rate of seven patients with progressive muscular dystrophy. Dr S P Goodhart placed the clinical material at our disposal.

METHOD

The studies were carried out with the aid of the cardi tachometer,² an instrument devised by one of us, which automatically records the heart rate of subjects for indefinite periods of time under all degrees of physical activity and rest. The action current of the heart is led from the chest by two electrodes, through 100 feet of light wire to a radio amplifier, which amplifies it about 6,000 times. The amplified current actuates a relay system, which in turn operates an electromagnetic counter by means of which the heart rate is counted. The subject can move about freely without interfering with the accuracy of registration. The patients were in one room, the apparatus and observers in another. Every effort was made to enable the subjects to carry on their usual daily routine so that we might obtain the daily curve of their heart rate. Every patient was studied on two separate occasions to insure complete adjustment to the novelty of the experimental conditions.

The experiments were begun in the late afternoon and continued until the following morning. The evening meal was served at 6 p m. During the course of the evening the patients conversed with one another, played cards, read and listened to a phonograph. Exercise tests were given. The response of the heart to emotion was studied by discussing with the patients some of their personal griefs or difficulties. The patients went to bed at their accustomed hour, and in the morning washed, dressed and ate breakfast. Soon after breakfast the experiment ended.

¹ Submitted for publication, July 10, 1930.

² From the Neurological Division, Montefiore Hospital for Chronic Diseases.

1 Goodhart, S P, and Globus, J H. On the Nature of Muscular Dystrophies. With a Report of Changes in Cardiac Muscle in Two Cases, *Neurol Bull* 1 386, 1918. Globus, J H. The Pathologic Findings in the Heart Muscle in Progressive Muscular Dystrophy, *Arch Neurol & Psychiat* 9 59 (Jan) 1923.

2 Boas, E P. The Cardi tachometer—An Instrument to Count the Totality of Heart Beats Over Long Periods of Time, *Arch Int Med* 41 403 (March) 1928.

During waking hours the heart rate was recorded every few minutes, and the activity of the patient was carefully noted. During sleep the rate was calculated for every half hour, except when the patient appeared disturbed or restless, when more frequent readings were made. Early in the morning the basal heart rate was recorded, that is, the heart rate in the postabsorptive resting state.

RESULTS

As a basis of comparison we used similar observations on the heart rates of 103 normal persons.³ In table 1 are recorded the heart rates in the cases of progressive muscular dystrophy, as well as the average heart rates in our series of normal persons. In most instances the heart rates of the patients with muscular dystrophy were higher in the first than in the second experiment. This is probably due to the fact that in the first experiments the patients were not fully at ease. In the table the figures given represent in each case the experiments in which the heart rates were lowest, as a rule, the second experiment.

Table 2 represents the protocol of an experiment on A. K., a man, aged 21 years, and the graphic record shows the heart rate during this experiment.

The striking feature in all of the cases is the tachycardia which is evident in the patients both waking and sleeping. For instance the male patients with muscular dystrophy had an average minimum sleeping rate of 70 and a basal rate of 82.5, compared to rates of 52.7 and 61.4, respectively, of the normal series.

A second characteristic of the heart rate in our cases of muscular dystrophy is its lability, its excessive acceleration in response to minimal stimuli. The intake of food, exercise and emotion caused the greatest quickening of the heart, while music, conversation and playing cards had little or no effect. Eating provoked a rise in rate of from 6 to 36 beats a minute. It was impossible to set one standard exercise for all of the patients because of their varying degrees of helplessness. We chose exercises in each case that involved the maximum use of the remaining functioning muscles, and encouraged the patients to work to the limit of their capacity. Such exercises caused a rise in heart rate from 11 to 30 beats a minute. It was difficult to elicit an emotional response in these patients. Accordingly, in only four instances did we observe an appreciable rise in heart rate of from 10 to 24 beats a minute. In many instances slight movements such as turning in bed or sitting up or such acts as micturition provoked considerable increases in the heart rate.

Others have noted the rapid labile heart rate in patients with progressive muscular dystrophy. Meerwein⁴ collected 480 cases of this disease.

³ Boas, E. P., and Goldschmidt, E. F. Studien mit dem Cardiotachometer über Frequenz und Rhythmus des Herzschlags, *Klin. Wchnschr.* **9** 1115, 1930.

⁴ Meerwein. Verhältnisse von Herz und Zunge bei den primären Myopathien, Dissert., Basle, 1904.

TABLE 1.—Record of the Heart Rates of Patients with Muscular Dystrophy and of the Average Heart Rates of Our Normal Patients

Case	Diagnosis	Age	Duration of Illness, Years	Degree of Muscular Involvement	Heart Rates Waking				Heart Rates Sleeping					
					Time of Observation		Maxim	Mini	Time of Observation		Aver	Maxim	Mini	
					Hr	Min			Basal	Hr				Min
Men														
M H	Progressive muscular dystrophy	25	10	Dresses self cannot walk	4	5	92.6	118.0	85.0	9	32	76.5	85.2	69.8
A P	Progressive muscular dystrophy	32		Dresses self walks little	1	34	89.3	122.0	85.0	8	14	80.0	90.8	70.7
A K	Progressive muscular dystrophy	19	12	Dresses self cannot walk	5	45	92.5	124.0	85.0	7	51	80.6	85.7	70.9
L S	Progressive muscular dystrophy	58	28	Helpless	5	6	74.4	101.0	70.0	9	39	68.4	78.0	61.1
A T	Progressive muscular dystrophy	21	13	Dresses self, walks little	2	48	89.7	111.5	85.0	9	9	74.1	83.0	69.0
D K	Progressive muscular dystrophy	15	7	Dresses self, cannot walk	5	7	94.3	128.5	85.0	7	52	84.1	88.5	78.7
Average		28	14				89.0	117.5	82.5			77.3	84.8	70.0
Normal average		28					77.8	111.8	61.4			59.4	71.1	52.7
S M	Charcot Marie tooth type of progressive muscular atrophy	15	8	Can walk	6	51	88.2	121.0	68.8	9	30	53.7	79.0	49.1
H G	Charcot Marie tooth type of progressive muscular atrophy	25		Walks with difficulty	1	17	88.8	126.0	73.4	8	5	75.7	85.4	68.6
J B	Arthritis deformans	39	2	Cannot walk	4	16	91.2	110.0	76.0	7	55	73.7	80.0	68.0
Women														
B G	Progressive muscular dystrophy	21	12	Completely helpless	5	4	91.8	115.0	83.0	8	0	77.5	82.5	68.1
Normal average		24					83.9	120.6	67.1	69.9		65.3	75.4	57.7
S G	Arthritis deformans	14	6	Walks on crutches	5	6	98.0	126.0	69.0	8	0	68.8	86.9	61.8
M S	Arthritis deformans	33	11	Completely helpless	1	42	93.1	108.5	77.0	8	3	75.0	85.1	68.7
B O	Polomyelitis (anterior)	14	12	Completely helpless	5	45	113.3	127.3	95.0	7	26	92.8	102.5	83.6

published before 1904. In 89 of these, some abnormality of the heart or pulse was noted. He divided these 89 into 4 groups. Group 1 consisted of 13 patients who had abnormal pulse rates but no cardiac murmurs or evidences of cardiac enlargement. Twelve of these patients had pulse rates that ranged from 90 to 135, and in 3 of them the rate was very labile. Group 2 consisted of 12 patients who had definite murmurs but no enlargement of the heart. Twelve of these had rapid pulse rates, and in 1 the pulse was very labile. Group 3 consisted of 49 patients who showed cardiac enlargement. Nineteen of them had rapid pulse rates. Group 4 represented 15 cases that came to necropsy in which definite lesions of the myocardium were found.

We have been able to find few records of the heart rates of patients with progressive muscular dystrophy in the literature since 1904. Globus⁵ observed a boy, aged 5, whose pulse was rapid and labile, varying from 80 to 130. Sacara-Tulbure⁶ noted a rapid pulse in several cases and irregular rhythm in three cases. Berblinger and Duken⁷ and Schliephake⁸ reported a number of interesting cases. The first, that of a boy, aged 12, when in the hospital showed a gradual increase in pulse rate from 80 to 120 in six days. Then the patient exhibited abdominal tenderness, vomiting and leukocytosis, while the pulse rate rose to 160. A laparotomy revealed no lesion, and the boy died shortly afterward. The second patient, a boy, aged 14, had attacks of pallor lasting from a few minutes to several days, in which the pulse rate rose from 80 to 160. An electrocardiogram, taken between attacks, showed a questionable conduction block. The third patient had definite attacks of paroxysmal ventricular tachycardia, proved electrocardiographically, and the authors suggested that the other two patients had a similar disturbance.

We noted no abnormalities of rhythm in any of our cases. Electrocardiograms were taken in all of them. Five showed essentially normal electrocardiograms, but A. F. showed left axis deviation with the T wave negative in leads 2 and 3 and the descending limb of R in leads 1 and 2 notched, while case L. S. showed left axis deviation with T in lead 1 negative, and the descending limb of R in lead 1 notched. These signs were accepted as evidence of myocardial damage. In these two cases their significance is lessened because A. F., though a young man, had hypertension (160 systolic and 100 diastolic), and L. S. was 58 years old.

⁵ Globus, J. H. (footnote 1, second reference)

⁶ Sacara-Tulbure. Contribution à l'étude clinique de la paralysie pseudo-hypertrophique, *Rev. de méd.* **14** 273, 1894.

⁷ Berblinger and Duken, J. I. Der kardio-intestinale Symptomenkomplex bei der progressiven Muskeldystrophie, *Ztschr. f. Kinderh.* **47** 1, 1929.

⁸ Schliephake, E. II. Graphische Untersuchungen der kardio-intestinale Symptomenkomplex bei der progressiven Muskeldystrophie, *Ztschr. f. Kinderh.* **47** 85, 1929.

Teleoioentgenograms were taken of all of the patients. None showed enlarged hearts, nor was the configuration of the heart typical. The blood pressure for all except A. F. was within normal range. A striking feature on auscultation in four of the patients was the feeble-

TABLE 2—*Protocol of the Observations on the Heart Rate of A. K.*

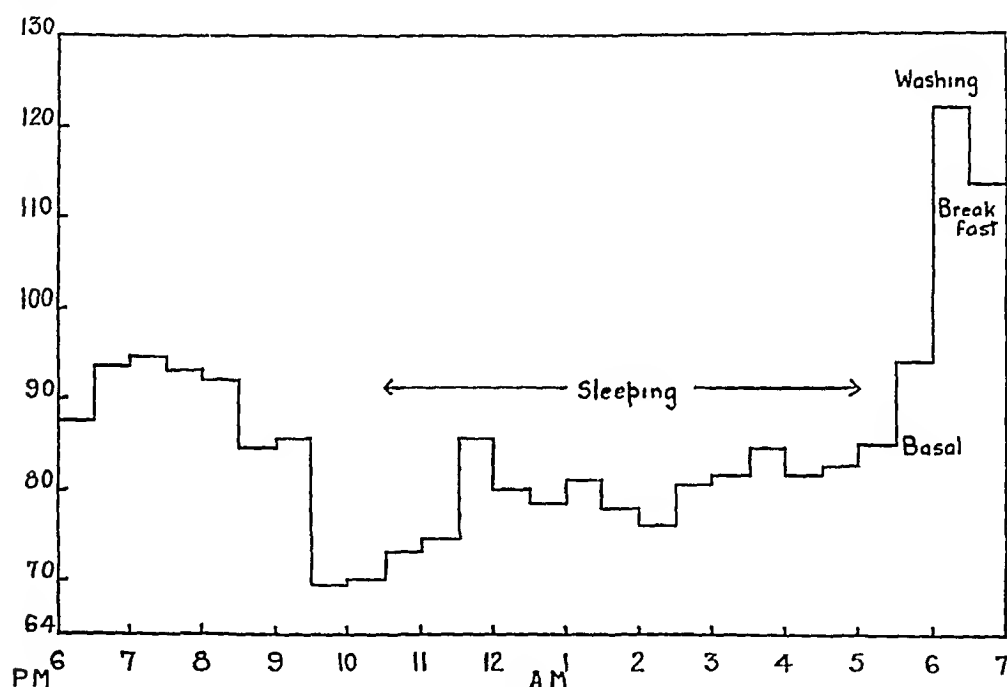
Time	Total Minutes	Counter Reading	Total Beats	Rate	Comment
P. M.	6 19	299			Sitting in chair
	6 20	385	86	86.0	Sitting in chair
	6 25	854	469	93.8	Sitting in chair
	6 30	1,288	429	85.8	Sitting in chair, reading
	7 00	4,093	2,810	93.6	Sitting in chair, talking
	7 13	5,312	1,219	93.7	Starting to play cards
	7 30	6,934	1,622	95.4	Playing cards
	8 00	9,728	2,794	93.1	Playing cards
	8 30	12,497	2,769	92.3	Sitting in chair, talking
	9 00	15,036	2,539	84.6	Sitting in chair
	9 16	16,403	1,367	85.4	Undressing, in bed
New start					Electrode moved, replaced with adhesive over strap
	9 21	16,729			Undressing
	9 22	16,813	84	84.0	Undressing
	9 30	17,580	767	95.8	In bed (awake)
	10 00	19,678	2,093	69.7	In bed (awake)
	10 07	20,143	470	67.1	Physical examination
	10 09	20,284	141	70.5	Physical examination ended
	10 30	21,773	1,489	70.9	Asleep
	11 00	23,973	2,200	73.3	Asleep
	11 30	26,309	2,336	74.5	Asleep
	12 00	28,880	2,571	85.7	Asleep
A. M.	12 30	31,279	2,399	79.9	Asleep
	1 00	33,645	2,366	78.8	Asleep
	1 30	36,070	2,425	80.8	Asleep
	2 00	38,417	2,347	78.2	Asleep
	2 30	40,707	2,290	76.3	Asleep
	3 00	43,130	2,423	80.7	Asleep
	3 30	45,584	2,454	81.8	Asleep
	4 00	48,117	2,533	84.4	Asleep
	4 30	50,687	2,570	85.6	Asleep
	5 00	53,221	2,534	84.4	
	5 30	55,666	2,445	81.3	
	6 00	58,149	2,483	82.7	
	6 30	60,708	2,559	85.3	
	6 40	61,567	859	85.9	
	6 41	61,652	85	85.0	
	6 42	61,738	86	86.0	
	6 43	61,819	81	81.0	
	6 44	61,904	85	85.0	Basal rate, 85
	6 45	61,980	85	85.0	
	6 48	62,258	269	89.6	
	6 50	62,448	190	95.0	Getting up, dressing
	6 52	62,637	189	94.5	
	6 55	62,940	312	104.0	
	6 56	63,067	118	118.0	
	6 57	63,168	101	101.0	
	6 58	63,292	124	124.0	
	7 00	63,505	213	106.5	
	7 02	63,734	229	114.5	
	7 05	64,092	353	119.3	
	7 07	64,328	236	118.0	
	7 11	64,776	448	112.0	Getting into chair
	7 12	64,897	121	121.0	In chair
	7 15	65,246	349	116.3	In chair
	7 21	65,936	690	115.0	Morning toilet, urinating
	7 35	67,575	1,639	117.0	Eating breakfast

ness and absence of muscular quality of the first heart sound at the apex, and the accentuation of the second sound at the base. The sounds in these patients resembled those heard in patients with recent coronary thrombosis. In three patients the heart sounds were normal. No murmurs were heard except in A. F., who presented a systolic murmur at

the aortic area. It may be significant that D K, in whom the poor muscular quality of the first sound was most striking, showed the most rapid heart rate.

In general, however, we were unable to correlate any cardiovascular physical observations, the extent of involvement of the striated muscles or the duration of the illness with the level of heart rate.

What is the cause of the rapid heart rate in patients with progressive muscular dystrophy? Simple tachycardia may be due to neurogenic factors. As one of us has shown in another communication,⁹ however, neurogenic tachycardia disappears during sleep. The minimum heart rate during sleep is measured at a time when the manifold extrinsic stimuli that affect the heart are at a minimum, and, so, most closely



Graphic record of the heart rate of A K during an experiment

represents the chronotropic activity of the heart. Since our patients all showed a high minimum rate during sleep, neurogenic factors cannot be solely responsible for the tachycardia.

Fever and an increased basal metabolic rate, as well as anemia or anoxemia, may also determine a rapid heart rate. None of these obtains in muscular dystrophy. The elimination of these factors makes it probable that the tachycardia is caused by some intrinsic cardiac disturbance. This conclusion finds ready support in the pathologic studies of Globus,² Goodhart and Globus,¹ Bunting,¹⁰ and Berblinger and Duken,⁷ who found

9 Boas, E. P., and Weiss, M. M. The Heart Rate During Sleep as Determined by the Cardi tachometer, *J. A. M. A.* **92** 2162 (June 29) 1929.

10 Bunting, C. H. Chronic Fibrous Myocarditis in Progressive Muscular Dystrophy, *Am. J. M. Sc.* **135** 244, 1908.

in the myocardium fibrosis and fatty infiltration and lesions resembling those of the striated musculature. Further confirmation of such changes in the muscles are found in two of our electrocardiograms and in the electrocardiograms of Beiblinger and Duken, as well as in the abnormal quality of the first heart sound noted by us.

There is one other possible factor that merits consideration. Tachycardia may be determined by a faulty distribution of blood in the vascular tree. The important factors here are the vasomotor tone and the efficiency of the pumping action of the striated muscles on the return flow of blood through the veins. Since so large a part of the musculature in these patients is functionless, the efficiency of the peripheral venous pump must be greatly diminished. It is an extreme illustration of the difference between "trained" and "untrained" persons. It is well known that the latter have more rapid and more labile heart rates than the former. In order to check this point, we studied the heart rates of six patients disabled by such diseases as arthritis deformans and extensive anterior poliomyelitis and two cases of the Charcot Marie tooth type of muscular dystrophy. The heart rates are recorded in table 1. It is apparent that these patients too have a tendency to rapid heart rates, although in none of them is there reason to believe in the existence of a myocardial lesion. We realize that these few cases are not conclusive, particularly because of the youth of three of the subjects.

SUMMARY

Seven patients with progressive muscular dystrophy exhibited tachycardia which persisted during sleep. We believe that the rapid heart rate is due to the characteristic myocardial lesions of this disease, as well as to the effect of the loss of the pumping action of the striated muscles on the venous return flow. Further evidence of myocardial injury was presented by two patients who had electrocardiograms characteristic of disease of the heart muscle and by four patients in whom the first heart sound was feeble.

REPORT OF A CASE

History.—A K, a man, aged 21, presented a case of progressive muscular dystrophy. As a baby he was dropped on the floor and severely injured. Since the age of 6 the arms and legs had been weak. When he was 7 years old, he was struck by a man who jumped off a motorcycle, he was unconscious for half an hour, but had no permanent injuries. After the accident he walked home, but on climbing the stairs, he found that his legs were much weaker, so that he had to pull on the banister with the right hand and rest the left hand on the left knee. This condition never improved. During the following years the muscular weakness became progressively worse, and he began to have difficulty in arising from a sitting posture. He had been unable to walk for six years before consulting us. He had occasional palpitation, and frequently complained of cold hands and feet.

Examination—Examination revealed a well nourished young man who could not sit without assistance. The lips were large, the tongue was hypertrophied, and the teeth showed a trophic disorder. The cranial nerves were normal. There was a flaccid paralysis of both the upper and the lower extremities in flexion. He could not raise the arms above the head, and could not flex the thighs. The serratus, latissimus dorsi and rhomboid major muscles were paralyzed. The pectoralis major was weak on both sides. Rotation of the head was also weak.

The heart was not enlarged, the first heart sound was faint, and the second sounds were accentuated at the base, the aortic being stronger than the pulmonic second sound. There were no murmurs. The blood pressure was 125 systolic and 80 diastolic. The electrocardiogram showed right axis deviation. Table 2 is the protocol of the observations on the heart rate for a period of twelve hours and sixteen minutes.

GASTRIC ACIDITY IN DIABETES MELLITUS

ITS CLINICAL SIGNIFICANCE BASED ON A STUDY OF ONE
HUNDRED CASES [†]

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Persons with diabetes are exposed to all the conditions to which non-diabetic persons are exposed, infectious as well as noninfectious. For the diagnosis of some of these conditions, studies of gastric acidity are frequently employed. Such conditions include gastric and duodenal ulcers, disease of the gallbladder and hepatic disease in general, malignant conditions, anemias, etc. Therefore, it is important to know whether diabetes, per se, may be responsible for disturbances of gastric acidity.

Working with the same disease daily, one can hardly fail to be impressed by various phenomena as they are met with from time to time, and the impression gained was that in diabetes not only does the gastric acidity tend to be lower than normal, but achlorhydria occurs frequently. In the interpretation of these observations, there is, however, an important variable to consider. Determination of gastric acidity is not part of the routine in the management of the diabetic person. It is made use of only when signs or symptoms suggest any one of the aforementioned conditions, namely, ulcer, cancer, etc. Therefore, the low gastric acidities observed in the past may have been the result of these associated conditions. Our records of diabetic patients fail to reveal an exceptional incidence of these conditions. There is, therefore, good reason to suspect that the relationship between lowered gastric acidity and diabetes is more causal than accidental.

The literature on this subject is scanty. Standard works on diabetes, such as those of von Noorden, Graham, Joslin, and others, make no mention of it. In the latest addition to the chapter on diabetes mellitus in Nelson's Loose-Leaf System of Medicine, Joslin referred briefly to the work of Wiechmann and Elzas. In a study of twenty-five cases of diabetes, these authors found achlorhydria in eight cases, an incidence

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* This investigation was made with the aid of a grant from Mr W W Butler of Montreal and a Governor of this hospital

of 32 per cent. Severity of the diabetes and acidity did not appear to be related. Joslin here also recorded his own experience, achlorhydria was found in nine cases of thirty-seven investigated, an incidence of approximately 25 per cent. Cammidge, in his work on "New Views on Diabetes Mellitus," referred to this subject briefly, and stated that "in some cases of frank diabetes with persistent hyperglycemia and evidence of defective formation of internal secretion of the pancreas, a study of the hemoglobin dissociation constant of the blood and carbon dioxide tension of the alveolar air has pointed to a deficient production of hydrochloric acid by the stomach." In 1926, Bowen and Aaron¹ reported the cases of ten diabetic patients suffering from diarrhea. Achlorhydria was found in every case. As it was suspected that the diabetes may have been responsible for the achlorhydria, an investigation of the gastric acidity was made in a number of other diabetic persons as well. In the whole group, sixty-nine cases, the incidence of achlorhydria was 29 per cent. The data also suggested that achlorhydria was related to the severity and the duration of the diabetes. No patient with achlorhydria was found who did not have severe diabetes. With regard to the duration of the diabetes, it was found that the average duration among the group with normal acidity was 2.8 years, with decreased acidity, it was 3.6 and with achlorhydria, 6.6 years. Relationship between mortality and achlorhydria was also suggested.

The aforementioned observations were considered sufficiently interesting to warrant further investigation. For this purpose, 100 diabetic persons were selected at random from our clinic. In none of these patients were there any signs or symptoms of digestive disorders. Though we adhered to selection of subjects at random otherwise, an attempt was made to make the group fairly representative with regard to age, and severity and duration of the diabetes.

TECHNIC

During the last decade, attempts have been made to improve the reliability of data with regard to gastric acidity. Thus, to insure stimulation of gastric secretion, there has been a tendency to replace the standard Ewald test meal, consisting of toast and tea, with histamine or alcohol. Fractional analysis has been substituted for single determinations and p_H determinations for estimation of titratable acidity. It is obviously not our purpose to decry any of these new procedures. They undoubtedly have their place, and may yield more reliable information than the single estimation of the titratable acidity of gastric juice obtained with the use of toast and tea. For example, histamine should be of particular value in differentiating between the two types of achlorhydria now recognized, namely, (1) the type in which the mucosa is capable of producing hydrochloric acid, but the

¹ Bowen, B. D., and Aaron, A. H. Gastric Secretion in Diabetes Mellitus. Report of Ten Diabetic Patients Who Had Diarrhea and Achlorhydria, *Arch. Int. Med.* **37**: 674 (May) 1926.

stimulus of the test meal given is not sufficiently powerful, and (2) the type in which there is true cessation of function of the hydrochloric acid-producing cells. Both alcohol and histamine eliminate one possible source of error, namely, the neutralization of hydrochloric acid by the ingested food materials. An error common to the use of alcohol and the Ewald meal, but chiefly to alcohol, because of the volume of liquid introduced into the stomach, is excess dilution of the gastric juice in the absence of normal motility. With such dilution, the low acidity noted would obviously be more apparent than real. Errors common to all methods and resulting from the insertion of a tube are (1) excess production of alkaline mucus, (2) excess production of alkaline saliva and swallowing the latter and (3) abnormal regurgitation of alkaline fluids (bile, pancreatic and intestinal juices) from the intestines. With regard to the latter phenomenon, it may here be observed that there is a normal amount of regurgitation. Babkin² has shown that the acid concentration of fresh gastric juice of man ranges between 0.4 and 0.5 per cent. The optimum and usual acidity that ranges between 0.15 and 0.2 per cent hydrochloric acid is the result of a mild grade of regurgitation of the aforementioned alkaline fluids from the intestines.

The preceding observations may be made with regard to the possible variables in the interpretation of gastric acidity. They demonstrate that with this test, as with all other laboratory procedure, it is important to have a sound knowledge of physiology besides manipulative skill, and it is our experience that when due consideration is given to all of these factors, including the time interval between the ingestion of food and the collection of juice, a single estimation of the gastric contents, obtained following the administration of the standard Ewald meal, yields reliable information in the majority of cases. The latter procedure was, therefore, our routine in this investigation.

Another, and rather important, reason for adhering to the aforementioned technic was that it is important to compare things which are comparable. Our purpose in this investigation was to compare the gastric juice of the diabetic person with that generally accepted as normal. Here it may be observed that the standards of acidity still used by clinicians with regard to the amounts of free hydrochloric acid and total titratable acidity are those that were obtained with the Ewald meal and single analysis. The following are, briefly, the statistical results of this investigation.

RESULTS

That the group was representative with regard to sex is shown by the fact that there were forty-four males and fifty-six females. Though a number of variables have to be considered in the interpretation of severity, for practical purposes we divided our patients into two groups, namely, (1) those who required insulin to control the diabetes and (2) those who did not. It may be observed that we excluded patients who required insulin temporarily and as an emergency measure only. This included patients with infections, those who had had operations, and others. Our cases were fairly representative with regard to severity. In forty-nine cases the patients were treated with insulin, and in fifty-one cases insulin was not required.

² Babkin, B. P. *Die aussere Sekretion der Verdauungsdrusen*, Berlin, Julius Springer, 1914.

Practically all decades, with the exception of the first, were represented, as shown by tables 1 and 2

In table 3 are shown the incidences of the different amounts of free hydrochloric acid and total acidities expressed as cubic centimeters of tenth-normal acid

TABLE 1—*Age Incidence*

Decade	Number of Cases
1 to 10	0
11 to 20	8
21 to 30	11
31 to 40	8
41 to 50	23
51 to 60	32
61 to 70	13
71+	5

TABLE 2—*Duration of Diabetes*

Duration, Years	Number of Cases
1 0	49
1 1 to 2 0	22
2 1 to 3 0	12
3 1 to 4 0	3
4 1 to 5 0	3
5 1+	11

TABLE 3—*Incidence of Free Hydrochloric Acid and Total Acidity*

Acidity, Cc Tenth Normal	Incidence	
	Free Hydro chloric Acid	Total Acidity
0	39	
1 to 10	24	22
11 to 20	20	14
21 to 30	8	13
31 to 40	5	10
41 to 50	3	11
51 to 60		18
61 to 70		10
71 to 80	1	
81 to 90		1
91 to 100	1	
101+		1

It will be observed that there was complete absence of free hydrochloric acid in 39 per cent of the cases, and that in more than 50 per cent the amounts found were definitely below normal. This also applies to the total titratable acidity, fifty-nine patients had total acidities corresponding to less than 40 cc of tenth-normal acid.

Table 4 shows that there was no relationship between the duration of the diabetes and acidity.

These results, therefore, differ from those reported by Bowen and Aaron. It is important, however, to consider the fact that the selection of cases by the latter authors and ours were not the same. Ours were selected at random, except that cases with signs and symptoms of digestive disturbances were excluded, whereas Bowen's group included ten cases of diarrhea.

The relationship between the severity of the diabetes and the total acidity (the average acidity being expressed as cubic centimeters of tenth-normal acid) was as follows. In the cases in which insulin was

TABLE 4—*Duration of Diabetes and Acidity*

Duration, Years	Average Acidity (Cc Tenth Normal)	
	Free Hydrochloric Acid	Total
10	9.3	30.5
11 to 20	11.3	36.5
21 to 30	14.8	44.6
31 to 40	2.0	4.0
41 to 50	11.2	38.0
51+	10.6	40.2

TABLE 5—*Relationship Between Age and Acidity*

Decade	Average Acidity (Cc Tenth Normal)	
	Free Hydrochloric Acid	Total
10		
11 to 20	13.0	34.0
21 to 30	7.3	28.2
31 to 40	19.2	43.4
41 to 50	10.0	34.2
51 to 60	9.3	33.9
61 to 70	9.9	36.0
71+	5.8	25.7

used, the average free hydrochloric acid was 10.5 and the average total acidity was 36.2, in the cases in which insulin was not used, the average free hydrochloric acid was 9.8 and the average total acidity was 32.3. Here, again, our data differ from Bowen's, but they agree with those of Wiechmann and Elzas, in that no relationship was found, the average amounts of free hydrochloric acid and total acidity were practically the same in the group treated with insulin as in the group that was not treated with insulin.

Table 5 shows the relationship between age and acidity.

In the interpretation of these data, one must consider the fact that even in normal persons beyond middle age (about the age of 50) both free hydrochloric acid and total acidity tend to be low. When this fact is considered, there appears to be little or no relationship between age and acidity. In other words, though the average amount of free hydro-

chloric acid and total acidity was lower than expected under normal conditions at all age periods, age, per se, appears to have no particular influence among diabetic persons

As to the relationship between the sex of the patients and acidity (average acidity being expressed in cubic centimeters of tenth-normal acid), the following results were noted. The average free hydrochloric acid was 14.1 in males and 7.1 in females and the average total acidity was 36.8 in males and 32.3 in females. It appears, therefore, that, on the average, both the free hydrochloric acid and the total acidity tended to be lower among the female than among the male patients.

In table 6 is shown the combined relationship between age, sex and acidity.

For the purpose of investigating the aforementioned relationship in greater detail, males and females were separately grouped and the average

TABLE 6—*Relationship Between Age, Sex and Acidity*

Decade	Male Average Acidity, Cc Tenth Normal		Female Average Acidity, Cc Tenth Normal	
	Free Hydro chloric Acid	Total	Free Hydro chloric Acid	Total
11 to 20	18.7	62.2	6.5	48.2
21 to 30	15.9	37.8	3.3	21.0
31 to 40	24.0	46.0	9.0	37.6
41 to 50	18.3	38.8	2.9	28.0
51 to 60	8.8	32.0	10.7	30.9
61 to 70	9.6	24.0	10.2	49.8
71+		13.0	6.5	28.8

age amounts of free hydrochloric acid and total acidities were calculated for the different decades. Here, again, though the average amount of both free hydrochloric and total acidity tended to be lower for all decades, age did not appear to be a factor, but the values in the group of females were lower than those of the males.

COMMENT

Repeated experiences of a number of workers have shown that achlorhydria may be found among normal persons. The incidence tends to be higher with single analysis than with periodic collection of gastric juice. Unfortunately, in a large part of the literature one finds an admixture of normal and abnormal persons in the groups investigated. On the whole, however, it would appear that with periodic examinations, the incidence of achlorhydria is approximately 10 per cent, and with single analysis only there is an additional 9 per cent, in other words, it would appear that with the use of the standard Ewald test the incidence of achlorhydria is about 20 per cent. In an analysis

of 100 normal persons, Bennet and Ryle³ found only four cases of complete absence of free hydrochloric acid. Our experience among non-diabetic persons with the Ewald test shows an incidence of achlorhydria of less than 20 per cent. However, allowing an incidence of 20 per cent, the latter value is only about one half of that found in the group of 100 diabetic persons investigated. Our results, therefore, appear to warrant the conclusion that gastric acidity tends to be low in diabetes. The clinical importance of this observation is that when diabetic persons show signs and symptoms that suggest conditions for the diagnosis of which gastric acidity is considered, the fact that diabetes, per se, may be responsible for low acidity must be considered.

This investigation does not concern cause and effect. That diabetes may be responsible for altered function of the gastro-intestinal tract is, however, suggestive. It is interesting to note that gastro-intestinal disturbances are not uncommon in this disease, in the absence of the usual causes. Thus, in addition to achlorhydria, diarrhea may be noted occasionally and constipation commonly, and "cramps," vomiting or dilatation of the stomach may be observed prior to the onset of coma. Hypertrophy of the duodenal mucosa is also a suggestive sign, this characteristic was an almost constant observation at autopsies, in cases of diabetic coma, prior to the days of the use of insulin. This phase of the subject is now being investigated.

3 Bennet, T. I., and Ryle, J. A. *Guv's Hosp Rep* 71:286 (July) 1921

THE METABOLISM OF GALACTOSE

I CONSIDERATIONS UNDERLYING THE USE OF GALACTOSE IN TESTS OF THE FUNCTION OF THE LIVER¹

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In 1901, Strauss¹ suggested the use of levulose for testing the function of the liver. Five years later, Richard Bauer,² of Vienna, introduced galactose for a similar purpose. While this phase of studies on the liver aroused considerable interest in England and on the continent, American literature on clinical medicine has given little consideration to the subject. American contributors have usually been concerned with levulose, while galactose has either been ignored or mentioned only with a word of condemnation. This is all the more strange since American biochemical literature is replete with contributions concerning the metabolism of this sugar.

While working with Bauer in 1927, one of us was impressed with the information obtained through studies on galactose tolerance in various conditions of the liver. For the past two years we have been utilizing this test at the Jewish Hospital of Philadelphia in an attempt to satisfy ourselves as to its value and to determine its limitations. The test used has consisted of the ingestion of 40 Gm of pure galactose on a fasting stomach, and the determination of the urinary output of galactose for the ensuing five hour period. Before presenting our clinical studies, we feel that certain basic considerations must be presented regarding the use of any sugar as a functional test substance. We shall attempt to show that galactose answers these basic considerations, comparing, wherever possible, its behavior to that of levulose, and finally, offering some observations on the metabolism of galactose.

^{*} Submitted for publication, Aug 22, 1930

[†] From the Gastro-Intestinal Clinic of the Jewish Hospital of Philadelphia
Presented at the College of Physicians, Section on Medicine, April 28, 1930

1 Strauss, H. Zur Funktionsprüfung der Leber, Deutsche med Wchnschr **27** 757, 1901

2 Bauer, R. Ueber die Assimilation von Galaktose und Milchzucker beim Gesunden und Kranken, Wien med Wchnschr **56** 20, 1906

REQUIREMENTS OF ANY SUGAR USED IN TESTING THE
FUNCTION OF THE LIVER

Purity of the Sugar —The sugar used must be obtainable in pure form. This has been possible in the case of galactose but not for fructose. Folin and Berglund³ found fructose so unstable that they questioned whether any is obtainable entirely free from the products of decomposition.

Absorption of the Sugar —If the sugar is to be given orally, it must be easily absorbed from the intestinal tract, thus eliminating the difficulties of loss by vomiting or diarrhea, and it must not be readily destroyed by bacteria in the intestine. Cori,⁴ studying the rate of absorption of hexoses and pentoses from the intestinal tract of rats, found that the loss of sugar due to bacterial action in the intestines was so small that it could be neglected in the experimental calculations. He also showed that the absorption of galactose, dextrose and fructose proceeds at a rate constant for each sugar, and that the ratio of these rates may be expressed as 110, 100 and 43 in the order mentioned. Thus, it is seen that galactose is absorbed at least 2.5 times as rapidly as fructose. This observation indicates that galactose is least likely to produce gastrointestinal disturbances and particularly loss by diarrhea, phenomena that Folin and Berglund³ as well as Rowe⁵ found frequently in the use of their fructose preparations. In no instance was bowel disturbance from the use of galactose noted by us, and in only one case was the sugar vomited, this occurred in a patient who was very ill with acute nephritis and toxic jaundice.

Tolerance for the Sugar —The normal tolerance for the sugar used must be known, and its utilization in relation to age, weight and sex must be considered. Cori⁶ found that the percentage of absorbed galactose excreted in the urine increased with increased length of absorption, in spite of the fact that the rate of absorption was constant, indicating that there is a definite amount of galactose that the liver is capable of utilizing at one time. Bauer,² Rowe⁵ and others have demonstrated that this normal tolerance for human beings is about 40 Gm. Rowe contended that the threshold of tolerance is higher for

3 Folin, O., and Berglund, H. Some New Observations and Interpretations with Reference to Transportation, Retention and Excretion of Carbohydrates, *J Biol Chem* **51** 213, 1922.

4 Cori, C. F. The Rate of Absorption of Hexoses and Pentoses from the Intestinal Tract, *J Biol Chem* **66** 691, 1925.

5 Rowe, A. W. Metabolism of Galactose. I. The Threshold of Tolerance in Normal Adults, *Arch Int Med* **34** 388 (Sept) 1924.

6 Cori, C. F. The Fate of Sugar in the Animal Body. III. The Rate of Glycogen Formation in the Liver of Normal and Insulinized Rats During the Absorption of Glucose, Fructose and Galactose, *J Biol Chem* **70** 577, 1926.

women than for men, he believed that woman entertains within her organism a specific galactose mechanism which, so far as is known, is absent in man. Rowe stated that this power of synthesis, of storage and of conjugation of galactose is inherent in the female mammary glands.

A study of table 1 will indicate that Rowe's contention is probably not justified. This table includes the results obtained in fifteen normal males and fifteen normal females, to each of whom the standard dose of 40 Gm of galactose was administered. In their respective columns are given the ages of the patients in years, the weights in pounds and

TABLE 1—*Comparative Study of Excretion of Galactose in Males and in Females*

Females			Males		
Age, Years	Weight, Pounds	Galactose* in Urine, Gm	Age, Years	Weight, Pounds	Galactose* in Urine, Gm
5	52	0.50	6	36	0.50
26	100	0.00	52	110	1.20
55	102	0.25	64	110	1.50
64	107	2.20	53	112	1.08
63	108	0.69	59	115	0.30
55	110	0.13	42	120	2.20
42	110	1.00	30	126	1.00
63	115	0.30	64	129	0.00
49	115	0.70	50	129	1.20
64	134	0.98	50	133	1.10
35	130	0.00	40	142	1.20
18	153	0.65	69	160	0.00
38	162	1.98	59	162	1.10
50	175	0.00	51	162	0.87
32	185	0.19	54	166	0.00
Average		0.64	Average		0.88

* Galactose output in the urine during the five hours following the ingestion of 40 Gm of that sugar.

the urinary output of galactose for the five hours following its ingestion, in grams. All the decades from the first to the sixth are included. When it is considered that the normal person may excrete in the urine from none to 3 Gm of sugar in the five hours after the administration of 40 Gm of galactose, it becomes evident from this table that there is practically no difference between the sexes in their tolerance for this sugar.

The objection raised by some authors that the use of arbitrary amounts of the sugar without regard to the weight and age of the patient may also be answered from the figures in table 1. It will be noted that while all of the figures for the urinary output ranged below 3 Gm, the subjects of greater weight not infrequently excreted more sugar than those of less weight. Moreover, this series of cases indicates the independence of the test as regards the age of the patient.

These facts find further confirmation by Schirokauer,⁷ by Stern,⁸ and by Meyer and Stern⁹ in studies on children ranging in age from 2 to 8 years. They found that the limits of assimilation for galactose in children are definitely comparable with those observed in the adult.

Convertibility of the Sugar to Glycogen—The sugar employed must be a glycogen builder, but preferably such a builder with difficulty. If so, the sugar will tax this function especially, and will be more apt to register distress with milder degrees of damage to the liver. Galactose answers both of these requirements. Perfusion experiments by Grube¹⁰ with liver of tortoises showed a direct utilization of galactose by the liver. Roubitschek¹¹ and Hurwitz and Bloomfield,¹² using lactose in experiments with animals poisoned with phosphorus and chloroform, respectively, concluded that galactose is a glycogen builder. While Cori and Goltz¹³ have shown that galactose, dextrose and fructose permeate the liver cells with the same ease, many observations indicate that, of the three, galactose is converted to glycogen the most slowly. Thus, Hoffmeister's¹⁴ experiments indicate that galactose and lactose are assimilated in the smallest degree as compared with dextrose, levulose and cane sugar. Cori¹⁵ stressed the difficulty with which galactose is converted into glycogen. The work of Blumenthal,¹⁶ of Strauss¹⁷ and of Voit¹⁸ further attested to the difficulty with which galactose is

7 Schirokauer, H. Der Zuckerstoffwechsel beim Lymphatismus der Kinder, *Jahrb f Kinderh* **79** 581, 1914

8 Stern, G. Diphtherie und Leberfunktion, *Med Klin* **15** 873, 1919

9 Meyer, S, and Stern, G. Ueber den Galaktosestoffwechsel im Sauglings und Kleinkindesalter, *Arch f Kinderh* **68** 241, 1920

10 Grube, K. Untersuchungen ueber die Bildung des Glykogens in der Leber, *Arch f d ges Physiol* **118** 1, 1907

11 Roubitschek, R. Alimentare Galaktosurie bei experimenteller Phosphorvergiftung, *Deutsches Arch f klin Med* **108** 225, 1912

12 Hurwitz, S H, and Bloomfield, A L. Tests for the Hepatic Function. Lactose Tolerance as Influenced by the Liver Necrosis of Chloroform Poisoning, *Bull Johns Hopkins Hosp* **24** 380, 1913

13 Cori, C F, and Goltz, H L. The Permeability of Liver and Muscles for Hexoses and Pentoses, *Proc Soc Exper Biol & Med* **23** 124, 1925

14 Hoffmeister, F. Ueber Resorption und Assimilation der Nahrstoffe. V. Ueber die Assimilationsgrenze der Zuckerarten, *Arch f exper Path u Pharmacol* **25** 240, 1888

15 Cori, C F. The Rate of Glycogen Formation in the Liver During the Absorption of Fructose and Glucose, *Proc Soc Exper Biol & Med* **23** 459, 1925

16 Blumenthal, F. Zur Lehre von der Assimilationsgrenze der Zuckerarten, *Beitr z chem Physiol u Path* **6** 329, 1904

17 Strauss, A. Leber und Glykosurie, *Berl klin Wchnschr* **35** 1121, 1898

18 Voit, C. Ueber die Glykogenbildung nach Aufnahme verschiedener Zuckerarten, *Ztschr f Biol* **28** 245, 1891

assimilated Foster¹⁹ found that the ingestion of from 40 to 100 Gm of galactose by normal adults produced a marked hyperglycemia, whereas moderate amounts of fructose failed markedly to alter the level of the blood sugar Bodansky²⁰ found that in twenty healthy dogs, the tolerance for levulose, as determined by analysis of the blood, was better than that for dextrose or galactose It is probable that fructose is converted into dextrose in the liver with such facility that it normally never gets beyond that organ This assumption is based on the fact that fructose does not appear in the urine of either normal or diabetic persons, even when large quantities of fructose or cane sugar

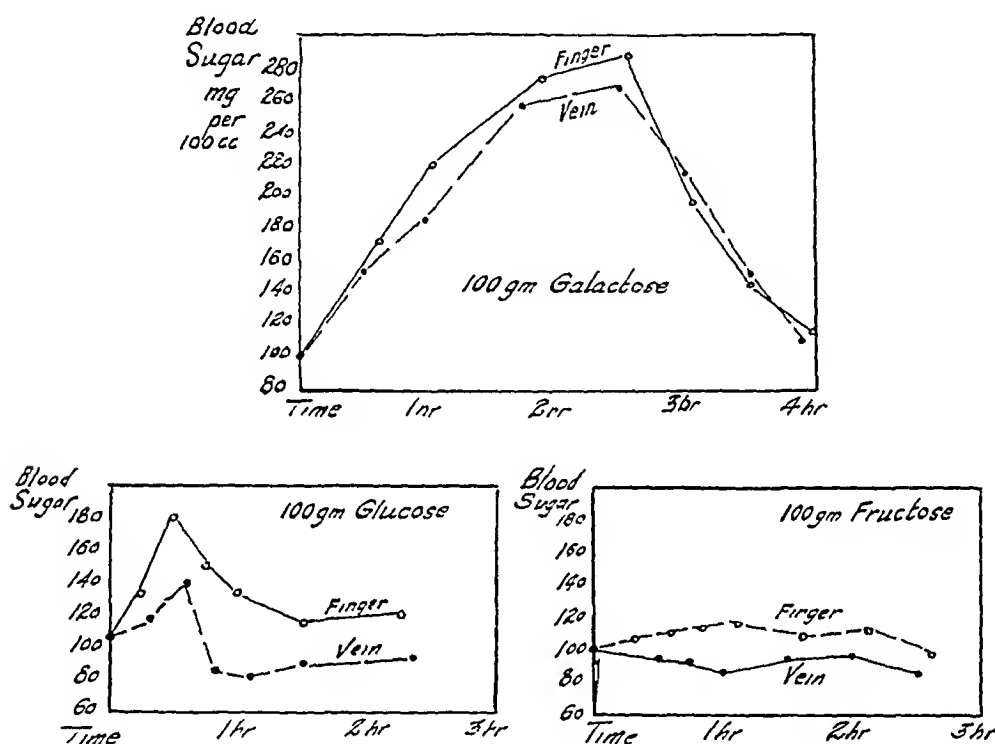


Chart reproduced from article by Foster showing a divergence of the venous and arterial curves after ingestion of dextrose and fructose, but practically a superimposition of the curves after the ingestion of galactose

have been taken Folin and Berglund³ stated that the limits of assimilation for levulose are so high that they can scarcely be exceeded As a glycogen builder, then, fructose is on a par with dextrose, galactose is such a builder with difficulty

Specific Utilization of the Sugar by the Liver—The sugar used must be specifically absorbed by the liver, and must not be utilizable, or only

19 Foster, G L Studies on Carbohydrate Metabolism I Some Comparisons of Blood Sugar Concentrations in Venous Blood and in Finger Blood, J Biol Chem 55 291, 1923

20 Bodansky, M Fructose, Glucose and Galactose Tolerance in Dogs, J Biol Chem 56 387, 1923

to a slight degree, when it reaches the general circulation Sachs²¹ and Blumenthal¹⁶ furnished experimental evidence showing that levulose and galactose are absorbed almost specifically by the liver Draudt,²² in animals with Eck fistulas, found an excretion of 79 per cent for those fed galactose, as compared with an excretion of from 4 to 10 per cent before operation There is convincing evidence in our own experiments as well as in those of others of the practical nonutilizability of galactose by the tissues after it passes the liver The accompanying chart is reproduced from an article by Foster,¹⁹ who first showed that the sugar content of blood from the finger-tips is practically identical with that of arterial blood A study of these charts of blood sugar curves after the ingestion of 100 Gm of dextrose, fructose and galactose reveals a divergence of the venous and arterial curves in the case of dextrose and fructose, but practically a superimposition of the curves after the ingestion of galactose This may be explained on the basis that practically no utilization of the galactose occurs during the passage through the muscles The experiments of Mann and Magath²³ add further convincing evidence, they found that the hypoglycemic reaction produced in their animals after extirpation of the liver could be relieved by the injection of certain substances, dextrose, maltose, mannose, dextrin and galactose, into the blood stream When dextrose was injected into an animal that was moribund because of the hypoglycemic state, recovery was usually complete in from one to four minutes, but the beneficial action of galactose was so slight and transient that it could scarcely be noted, unless the animal were under the closest observation, again indicating that the tissues, without the liver, utilize galactose to a very slight degree, if at all A study of table 2 in our own experiments with galactose confirms this contention strongly Table 2 presents the output of blood sugar and the urinary sugar at one-half, one, two and three hour intervals after the ingestion of 40 Gm of galactose, and similar figures for a subsequent day when the patient ingested 40 Gm of galactose and simultaneously was given a hypodermic injection of 10 units of insulin Of particular interest is the fact that in spite of the markedly lowered curves for blood sugar after the injection of insulin, sugar was still excreted in the urine in amounts definitely comparable to those excreted when no insulin was used

21 Sachs, H Ueber die Bedeutung der Leber für die Verwerthung der verschiedenen Zuckerarten im Organismus, *Ztschr f klin Med* **38** 87, 1899

22 Draudt, L Ueber die Verwertung von Laktose und Galaktose nach partieller Leberausschaltung (Ecksche Fistel), *Arch f exper Path u Pharmakol* **72** 457, 1913

23 Mann, F C, and Magath, T B The Effect of the Administration of Glucose in the Condition Following Total Extirpation of the Liver, *Arch Int Med* **30** 171 (Aug) 1922

This excretion of galactose occurred in spite of a definite hypoglycemia with the attending symptoms of marked sweating, weakness, intense hunger, etc. In the case of F L, for example, in which the amount of blood sugar ranged between 57 and 65 mg for the first and second hours, the urinary excretion of galactose was still 772 mg. The same result may be noted with the other cases of the group. These observations can be interpreted only as an indication that the tissues, even when sorely in need of sugar, cannot utilize galactose to any notable degree. These observations have some significance from another standpoint. Folin and Berglund³ expressed the belief that absorption of sugars

TABLE 2—*Output of Sugar at Intervals After the Ingestion of Galactose and After the Ingestion of Galactose Accompanied by the Injection of Insulin*

Patient	Galactose, 40 Gm		Galactose, 40 Gm Plus Insulin, 10 Units		Patient	Galactose, 40 Gm		Galactose, 40 Gm Plus Insulin, 10 Units	
	Blood Sugar, Mg	Urine Sugar, Mg	Blood Sugar, Mg	Urine Sugar, Mg		Blood Sugar, Mg	Urine Sugar, Mg	Blood Sugar, Mg	Urine Sugar, Mg
M S					A D				
Fasting	166	0 0	115	0 0	Fasting	88	0 0	68	0 0
½ hour	192	73 2	125	52 8	½ hour	136	283 6	75	185 6
1 hour	206	618 8	100	32 5	1 hour	166	954 6	57*	500 0
2 hours	172	0 0	45*	126 0	2 hours	86	206 2	47	134 4
3 hours	138	0 0	63	0 0	3 hours	86	0 0		0 0
Total		692 0		211 3	Total		1,444 4		820 0
F L					J D				
Fasting	88	0 0	88	0 0	Fasting	100	0 0	86	0 0
½ hour	146	75 0	86	No spec	½ hour	176	319 5	111	400 0
1 hour	150	475 0	65	No spec	1 hour	150	414 0	55	612 7
2 hours	86	800 0	57*	772 7	2 hours	94	0 0	50	0 0
3 hours	81	130 0	53	204 0	3 hours		0 0		0 0
Total		1,480 0		976 7	Total		733 5		1,012 7

* Hypoglycemic reaction (c g, marked sweating, intense hunger, weakness)

by the tissues is the primary method of the body in reducing their concentration in the blood. They stated further that normally there is neither fructose nor galactose in the tissues, and that within this enormous empty reservoir, the galactose disappears as readily as does fructose, and more readily than dextrose. Cori, Pucher and Bowen²⁴ have shown that insulin increases the intake of sugar by the muscles. Trimble,²⁵ as well as Thalheimer,²⁶ reported experiments indicating that

24 Cori, C F, Pucher, G W, and Bowen, B D. Comparative Study of the Blood Sugar Concentration in the Arterial and Venous Blood of Diabetic Patients During Insulin Action, *Proc Soc Exper Biol & Med* **21** 122, 1923.

25 Trimble, H C, quoted by Joslin, E P. *Treatment of Diabetes Mellitus*, Philadelphia, Lea & Febiger, 1928, p 195.

26 Thalheimer, quoted by Joslin, E P. *Treatment of Diabetes Mellitus*, Philadelphia, Lea & Febiger, 1928, p 195.

the amount of sugar in the blood is invariably higher than that in the skin or muscles. If one considers these two last mentioned facts, one finds it impossible to reconcile the figures in table 2 with the statements of Folin and Berglund, so far as galactose is concerned. The exclusion of the muscles and other body tissues as important utilizors of galactose becomes of the highest importance if one is to justify the use of galactose for testing the carbohydrate function of the liver.

To establish further the use of galactose in this capacity, it becomes necessary to determine whether the blood or the urine offers the more accurate method for ascertaining its use by the liver. At first, one

TABLE 3—*Studies of the Blood and Urine of Four Persons After the Ingestion of Forty Grams of Galactose and on a Subsequent Day After Forty Grams of Dextrose*

Patient M M	Galactose, 40 Gm		Dextrose, 40 Gm		Patient H G	Galactose, 40 Gm		Dextrose, 40 Gm	
	Blood Sugar, Mg	Urine Sugar, Mg	Blood Sugar, Mg	Urine Sugar, Mg		Blood Sugar, Mg	Urine Sugar, Mg	Blood Sugar, Mg	Urine Sugar, Mg
Fasting	103	0 0	96	0 0	Fasting	120	0 0	91	0 0
½ hour	125	363 9	146	0 0	½ hour	136	90 0	142	0 0
1 hour	176	741 6	75	0 0	1 hour	154	800 0	182	0 0
2 hours	100	336 3	77	0 0	2 hours	96	100 0	68	0 0
3 hours	91	0 0	75	0 0	3 hours	81	0 0	64	0 0
Total		1,446 8			Total		990 0		
Patient F M					Patient M S				
Fasting	81	0 0	88	0 0	Fasting	166	0 0	120	0 0
½ hour	136	540 0	206	0 0	½ hour	192	73 2	192	0 0
1 hour	115	1,590 0	130	0 0	1 hour	206	618 8	272	0 0
2 hours	91	0 0	77	0 0	2 hours	172	0 0	222	882 5
3 hours	86	0 0	77	0 0	3 hours	138	0 0	168	133 0
Total		2,130 0			Total		692 0		1,015 5

would say the blood. However, since there is no accurate method for determining small quantities of galactose in the blood, it is obvious that estimations of blood sugar would indicate variations in all of the reducing substances in the blood, with no indication of which part was due to galactose. This fact is probably responsible for the discrepancies in the studies with galactose that have been based on blood sugar curves.

Then could the urinary output of galactose be used as a measure of its utilization? Before this question can be answered, two factors must be considered and their effects determined: (1) the effect of kidney threshold on the excretion of galactose, and (2) the effect of endocrine disturbances on the utilization of galactose.

KIDNEY THRESHOLD AND EXCRETION OF GALACTOSE

It is obvious that if urinary output is to be taken as a measure of the utilization of galactose, changes in kidney threshold might play an important part in the interpretation of the results. Table 3 shows

studies on the blood and urine sugar in four persons examined one day after the ingestion of 40 Gm of galactose and on a subsequent day after the ingestion of 40 Gm of dextrose. We were fortunate in that this group included one case (F M) with a high kidney threshold for dextrose. Examination of the table indicates, however, that this increased threshold did not hold for galactose. The cases of M M and H G indicate the differences that exist between the kidney thresholds for these two sugars, that of M S, a diabetic patient, illustrates the apparent lack of relationship of the blood sugar curve after the ingestion of galactose to the quantity excreted in the urine, it is of interest to compare the sugar curves and the output of urinary sugar in the other three cases.

Theoretic states of increased or decreased kidney threshold may readily be produced. Thus, experimental nephritis or the injection of insulin produces conditions comparable to an increased kidney threshold. The injection of epinephrine, on the other hand, produces a state fairly comparable to a decreased renal threshold. Corley,²⁷ after the injection of insulin into his animals, has shown a striking rapidity of disappearance of galactose from the circulation, without, however, affecting the amount of galactose lost in the urine. Cori,⁶ producing a tartarate nephritis in animals, involving a complete retention of dextrose, was unable to notice any effect on the rate at which circulating galactose disappeared from the blood. Returning to table 2, one may further study the effect of the injection of insulin on the excretion of galactose in the human subject. When one considers that after the ingestion of 40 Gm of galactose, the normal person may excrete from none to 3 Gm in the urine in the subsequent five hour period, and further, that the quantity excreted may vary, within these limits, in the same person from day to day, it is obvious that the differences in the urinary output with and without insulin (table 2) fall within the limits of normal variation. It is also to be noted that in the case of J D, the urinary output was higher with the injection of insulin than without it, in spite of the lower blood sugar curve. Here again is stressed the independence of the urinary output of galactose and the blood sugar curve.

The next consideration is the effect of the injection of epinephrine. Table 4 indicates the observations on blood and urinary sugar in four patients after the ingestion of 40 Gm of galactose, and the same determinations on a subsequent day after the ingestion of 40 Gm of galactose and the subcutaneous injection of 1 cc of epinephrine. It is interesting to note that in the two cases, F M and F L in which the epinephrine raised the amount of blood sugar little, if at all, above the kidney

²⁷ Corley, R C. The Disposal of Intravenously Administered Galactose in the Rabbit, *J Biol Chem* **74** 1, 1927.

threshold for dextrose the urinary output did not exceed that in which the galactose alone was given. In the other two instances, in A D and J D, the urinary sugar output was considerably higher, however, after fermentation with specially prepared yeast, the readings for the output of galactose were less than those for the excretion when epinephrine was not injected. J D, particularly, shows a marked difference before and after fermentation. It will be noted that in every instance the

TABLE 4—*Studies on Sugar in the Blood and Urine After the Ingestion of Galactose and After the Ingestion of Galactose and the Subcutaneous Injection of Epinephrine*

Patient A D	Galactose, 40 Gm		Galactose, 40 Gm Plus Epinephrine, 1 Cc		Patient F M	Galactose, 40 Gm		Galactose, 40 Gm Plus Epinephrine, 1 Cc	
	Blood Sugar, Mg	Urine Sugar, Mg	Blood Sugar, Mg	Urine Sugar, Mg		Blood Sugar, Mg	Urine Sugar, Mg	Blood Sugar, Mg	Urine Sugar, Mg
Fasting	88	0 0	60	0 0	Fasting	103	0 0	88	0 0
½ hour	136	283 6	200	30 0	½ hour	125	368 9	182	692 5
1 hour	166	954 6	214	662 5	1 hour	176	741 6	192	332 0
2 hours	86	206 2	120	521 0	2 hours	100	336 3	125	40 5
3 hours	86	0 0		248 0	3 hours	91	0 0	107	10 0
4 hours		0 0		202 3	4 hours		0 0		0 0
Total sugar		1,444 4		1,083 8	Total sugar		1,446 8		1,075 0
Total galactose†		1,444 4		1,260 5	Total galactose†		1,446 8		1,042 0
Patient J D					Patient F L				
Fasting	100	0 0	94	0 0	Fasting	88	0 0	79	0 0
½ hour	176	519 5	182	131 2	½ hour	146	75 0	142	119 9
1 hour	150	414 0	286	1,140 0	1 hour	150	475 0	172	318 2
2 hours	94	0 0	222	1,026 1	2 hours	86	800 0	130	142 5
3 hours		0 0	94	227 6	3 hours	81	130 0	81	0 0
4 hours		0 0	48*	0 0	4 hours	91	0 0	67	0 0
Total sugar		733 5		3,124 9	Total sugar		1,480 0		580 6
Total galactose†		733 5		115 0	Total galactose†		1,480 0		580 6

* Hypoglycemic reaction

† After fermentation with yeast specially prepared

urinary excretion of galactose is less after the injection of epinephrine than before. This may be mere coincidence, and four cases are not sufficient as a basis for an opinion, but is it not possible that, through the glycolytic action of the epinephrine on the liver more room is left, so to speak, for a more complete utilization of the galactose by the liver? A phenomenon of interest occurred in J D after the injection of epinephrine, between the third and fourth hours, the patient showed definite symptoms of a hypoglycemic reaction, and the readings for blood sugar at the fourth hour indicate the reason for this. Such a reaction must be kept in mind when epinephrine is administered.

On the evidence presented, we believe that there is no kidney threshold for galactose. This opinion is shared by Rowe and Chandler,²⁸ and finds confirmation in the observation of excretion of sugar after very small doses of galactose in the experiments of Folin and Beiglund.³ Regarding fructose, the last-named authors concluded that it has a renal threshold comparable to that of dextrose. Bodansky²⁰ reached a similar conclusion with experiments on animals, and Spence and Brett,²⁹ after a clinical study, discarded fructosuria as a measure of hepatic function because of the renal threshold involved.

THE GLANDS OF INTERNAL SECRETION AND THE METABOLISM OF GALACTOSE

The objections, on theoretical grounds, raised by Bloomfield and Hurwitz³⁰ to the utilization of carbohydrates in work on the function of the liver can be readily offset. These authors claim that hypophyseal, thyroid, pancreatic, suprarenal and neurogenic conditions may effect the metabolism of the sugars. The effect of insulin on the utilization and excretion of galactose has been indicated in table 2. As to the action of the other glands of internal secretion on the metabolism of galactose we quote from Solis-Cohen and Githen's textbook on pharmacotherapeutics, "Adrenalin produces a hyperglycemia which is due to the mobilization of glycogen, the store of which is diminished, and also, in part, to increased formation of glucose from proteins. Thyroid increases the response of the system to adrenalin, while thyroid secretion is decreased under the influence of pituitary administration."

It is evident from these facts that the effect of the glands of internal secretion on the metabolism of carbohydrate, insulin excepted, is dependent, directly or indirectly, on the suprarenals. Having shown the absence of any important effect of epinephrine on galactose excretion (table 4), one may disregard the relationship of endocrine disturbances in utilizing galactose in studies on the function of the liver. Analyzing Rowe and Chandler's²⁸ forty-four cases in which studies with galactose were performed on a few normal persons and on a variety of persons with endocrine disturbances, we find that in only one case did the urinary excretion reach 3 Gm. These authors did not state whether they attempted to differentiate between dextrose and galactose in this case.

28 Rowe, A. W., and Chandler, J. Metabolism of Galactose. Blood Sugar Curves, *Endocrinology* 8: 803, 1924.

29 Spence, J. C., and Brett, P. C. The Use of Levulose as a Test for Hepatic Insufficiency, *Lancet* 2: 1362, 1921.

30 Bloomfield, A. L., and Hurwitz, S. H. Tests for Hepatic Function. Clinical Use of the Carbohydrates, *Bull. Johns Hopkins Hosp.* 24: 375, 1913.

SUMMARY

Briefly, we may state that in galactose we believe we have demonstrated a sugar that is suitable for the testing of the function of the liver. This conclusion is based on the aforementioned studies on the metabolism of galactose. To recapitulate:

- 1 It is obtainable in pure form
- 2 It is readily absorbed from the digestive tract
- 3 It is converted into glycogen by the liver with some difficulty as compared to other sugars (dextrose and fructose)
- 4 It is practically not utilizable by any other tissues than the liver
- 5 After it reaches the general circulation, it is excreted in the urine regardless of either the state of the renal excretory mechanism or the activity of the endocrine glands

CUTANEOUS REACTIONS TO HISTAMINE

REACTIONS IN OCCLUSIVE AND SPASTIC VASCULAR DISEASE
AND IN CHRONIC INFECTIOUS ARTHRITIS^{*}

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The characteristic cutaneous reaction to histamine was described by Eppinger¹ and by Sollmann and Pilcher². A small area of the skin is cleansed with alcohol and is allowed to dry. A drop of 1:1,000 solution of histamine acid phosphate is placed thereon and is introduced intradermally by pricking with a fine needle. The excess histamine is gently wiped away with a piece of gauze. The reaction is characterized by a triple response, namely (1) a reddish-purple spot due to local capillary dilatation, (2) a local wheal, due to transudation of serum from the capillaries by reason of increased permeability, and (3) a flare due to dilatation of the arterioles by the reflex of a local axon.

Dale and Richards³ showed that the presence of small amounts of epinephrine and oxygen are necessary for the characteristic action of histamine to take place. Krogh⁴ expressed the belief that unknown factors may vary the formation of the wheals. Alexander and his co-workers⁵ showed that formation of wheals is greater over the trunk than over the extremities and that there is a substance present in the skin which augments the usual action of histamine, he suggested that the difference in the size of wheals over the trunk and over the extremities may be due to the presence of different amounts of this substance.

^{*} Submitted for publication, Aug 13, 1930

^{*} From the Division of Medicine, the Mayo Clinic

1 Eppinger, H, quoted by Lewis. Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1927

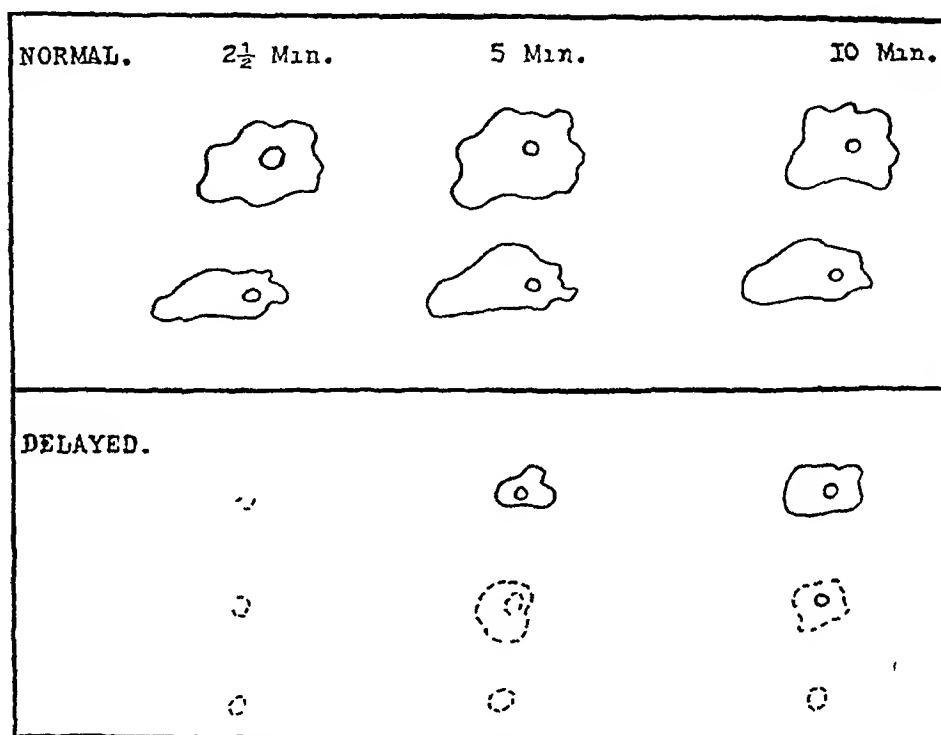
2 Sollmann, Torald, and Pilcher, J D. Endermic Reactions, J Pharmacol & Exper Therap 9 309 (March) 1917

3 Dale, H H, and Richards, A N. The Vasodilator Action of Histamine and of Some Other Substances, J Physiol 52:110 (July) 1918

4 Krogh, A. The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1929, p 208

5 Alexander, H L, Harter, J O, and McConnell, F S. Observations on the Formation of Wheals. II Comparison of Wheals Induced by Allergens and by Histamine, Proc Soc Exper Biol & Med 27 484 (March) 1920. Alexander H L, Weaver, W K, and McConnell, F S. III The Participation of an Unidentified Tissue Substance, *ibid*, p 486

Lewis⁶ described in detail the cutaneous reaction to histamine and the conditions under which it may vary. The reaction may be reduced by local injury, by the application of extreme heat or cold, by the local injection of epinephrine or solution of pituitary and over the sites of telangiectasis or nevi. Lewis described a diminished reaction when the blood supply is deficient. Starr⁷ made clinical application of the cutaneous reaction to histamine and showed that the response is reduced, delayed or incomplete in occlusive vascular disease.



Extent of cutaneous reactions to histamine

In this study, normal persons, patients with thrombo-angitis obliterans and arteriosclerosis who gave clinical evidence of impairment of circulation in the extremities and patients with Raynaud's disease, scleroderma and chronic arthritis were tested. The cutaneous reaction

6 Lewis, Thomas. Vascular Reactions of the Skin to Injury, Irresponsive Condition of Vessels with Special Reference to the Pathology of Telangiectases and Allied Conditions, *Heart* **13** 153 (Sept.) 1926, *Blood Vessels of the Human Skin and Their Responses*, London, Shaw & Sons, 1927, pp 70 and 242. Lewis, Thomas, Grant, R. T., and Marvin, H. M. Vascular Reactions of the Skin to Injury, Intervention of a Chemical Stimulus Illustrated Especially by Flare Response to Faradism, *Heart* **14** 139 (Dec.) 1927.

7 Starr, I., Jr. Changes in the Reaction of the Skin to Histamine as Evidence of Deficient Circulation in the Lower Extremities, *J. A. M. A.* **90** 2092 (June 30) 1928.

to histamine was determined arbitrarily over the wrists and ankles and sometimes over the knees. The wheals and flares were sketched at intervals of two and a half, five and ten minutes. In general, the wheals and flares were fully developed at the end of two and a half minutes, and delay beyond this time was classified as delayed reaction and was considered evidence of decreased circulation. Two types of abnormal reaction were noted: (1) simple delay in the full development of the wheal and flare, and (2) delay associated with reduced or incomplete wheal and flare, this occurred in cases in which there was greater deficiency in circulation, as shown in the accompanying illustration.

Ten normal persons were employed as controls. Some of these persons had cold extremities objectively, and others had warm extremities. In all, the wheals and flares were fully developed at the end of two and a half minutes. Since the intensity of the flare varied from 1 to 3 when graded on a basis of 1 to 4, and since there was likewise slight variation in the size of the wheal, it was felt that the time of appearance of the wheal and flare was of more significance than the size of the wheal and the intensity of the flare. Hence, the reaction was not interpreted to mean deficiency in circulation, unless there was delay beyond two and a half minutes in the full development of the wheal and flare.

In each of nine cases of occlusive vascular disease of the extremities, comprising instances of thrombo-angitis obliterans and arteriosclerosis, the cutaneous reaction to histamine was markedly delayed and reduced, and the greater the impairment of circulation the more the reaction was reduced. These results confirm those of Stair, who reported similar phenomena. De Takats and his coworkers⁸ also expressed the belief that delayed, reduced and incomplete reactions of the skin to histamine are of value in determining the decreased arterial flow.

In the group of spastic vascular disorders there were three cases of scleroderma, one of Raynaud's disease and one of a vasomotor neurosis of the Raynaud type. In all, the cutaneous reaction to histamine was delayed and reduced. Then resection of sympathetic ganglions and trunks was done in three of the five cases to release the spastic blood vessels. The indications for this operation and the results have been considered by Adson and Brown⁹ and by Adson and Rowntree¹⁰. In

8 De Takats, G., Quint, H., Tillotson, B. I., and Crittenden, P. J. The Impairment of Circulation in the Varicose Extremity, *Arch. Surg.* **18** 671 (Feb.) 1929.

9 Adson, A. W., and Brown, G. E. Thoracic and Lumbar Sympathetic Ganglionectomy in Peripheral Vascular Diseases. Therapeutic Value, *J. A. M. A.* **94** 250 (Jan. 25) 1930.

10 Adson, A. W., and Rowntree, L. G. Surgical Indications for Sympathetic Ganglionectomy and Trunk Resection in the Treatment of Chronic Arthritis, *Surg. Gynec. Obst.* **50** 204 (Jan.) 1930.

one case of scleroderma slight improvement in the reaction, that is, less delay, was noted following resection of the cervicothoracic and lumbar sympathetic ganglions and trunks, and this was taken to indicate an increased blood supply to the skin. The second case of scleroderma was associated with Raynaud's disease. At the time of observation, resection of the cervicothoracic and lumbar ganglions and trunks had been done, the former, four months previously and the latter, twelve days previously. There had been marked subjective and objective improvement, although some evidence of scleroderma remained, especially over the hands. There was a slight delay in the formation of the wheal and flare over the wrists. Over the ankles the wheal developed as in a normal person, but the flare was markedly delayed. In the third case of scleroderma, the reaction was markedly reduced and delayed. Operation was not done. In the case of Raynaud's disease, the same reaction as that of a normal person was obtained seven days after resection of the ganglions and trunks. The operation was not done in the case of vasomotor neurosis of the Raynaud type. Thus, in each of the cases of spastic vascular disease in which operation was done less delay or no delay in the cutaneous reaction to histamine was noted coincident with an increased supply of blood.

The test was used in twenty-seven cases of chronic infectious arthritis. The duration of the disease varied from six months to twelve years. The degree of involvement of the joints varied from that of the early stages to gross deformities, some subjects had cold extremities, and others had warm extremities. There was no correlation between the temperature of the extremities, the stage of the disease and the degree of formation of the wheals. Fifteen patients did not undergo resection of the ganglions and trunks. Of these fifteen cases the flare was slightly delayed in two, whereas the wheal developed within the usual time. In four other cases, the reaction as a whole was delayed over the ankles. In two of these four, the reactions seen in normal persons were present over the wrists and knees, even though the arthritis affected the wrists and knees to a greater degree. Twelve patients were operated on, of these, eight were tested after operation only. In all, full development of the wheal took place within the usual limits of time. In three of four cases observed both before and after operation, there was an abnormal reaction. In one case, there was a delay in the reaction as a whole, and the reaction improved slightly after resection of the lumbar sympathetic ganglions and trunks. In the second case there was only a slight delay in the flare, and a normal wheal and flare were obtained postoperatively. In the third case, reaction was delayed, and, since the diagnosis was chronic infectious arthritis of the vasospastic type, the condition probably should be classed with the vasospastic diseases associated with arthritis. After resection of the sympathetic ganglions and

trunks, the skin reacted normally to histamine. After operation the flare was delayed or absent in six of the twelve cases. In four cases in which a postoperative flare was obtained within the time required by normal persons, the test was not repeated after the seventh day. In one case a flare of the type seen in normal persons was obtained on the thirteenth day, in one on the sixtieth day and in one on the one hundred and fiftieth day. According to Lewis, the flare is lost about the sixth day after section of the cutaneous nerves, but it may persist for a week or more. In this small series, the flare had usually disappeared by the seventh postoperative day, but it was persistent in a few instances, lasting even to the one hundred and fiftieth day.

SUMMARY AND CONCLUSIONS

1 The cutaneous reaction to histamine, especially the time which elapses between administration of the drug and the formation of wheals, is of value in determining whether or not the blood supply to the skin of the extremities is reduced.

2 The reaction is delayed and reduced in occlusive vascular disease.

3 The reaction is delayed and reduced in the spastic phase of Raynaud's disease and in scleroderma.

4 Improvement is noted in the reaction coincident with an increased supply of blood after resection of the sympathetic ganglions and trunks in Raynaud's disease and scleroderma.

5 The reaction is occasionally reduced in chronic infectious arthritis, and the degree of the involvement of the joints or the temperature of the extremity appears to have no effect on the time of formation of the wheals.

6 When the formation of wheals preoperatively resembled that seen in normal persons, no change was noted in the time or size of formation of the wheals following resection of the sympathetic ganglions and trunks in chronic infectious arthritis. In the instances in which formation of the wheal was delayed preoperatively, there was improvement following resection of the sympathetic ganglions and trunks.

7 The flare usually is absent or reduced by the seventh day after resection of the sympathetic ganglions and trunks, but the usual flare may be persistent and may be present at least to the one hundred and fiftieth day.

GRANULOCYTOPENIA AND AGRANULOCYTIC ANGINA WITH RECOVERY

REPORT OF EIGHT CASES WITH FOUR RECOVERIES

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The syndrome described by Werner Schultz¹ in 1922 and previously mentioned by Turk² in 1907 has been reported frequently in the last three years. In 1927, Kastlin³ found forty-three cases in the literature. From June, 1927, to March, 1930, more than ninety cases were reported. The original syndrome described by Schultz as agranulocytosis and later named agranulocytic angina by Friedemann included an acute onset, usually in a woman, with a course marked by ulceration of the mouth or throat, leukopenia characterized by a considerable decrease or absence of granular cells and a normal red cell and platelet count, with death as the result. Some of the cases reported since do not coincide in all particulars with the syndrome originally described, since some occurred in males, in some there was involvement of the throat, and in some there were hemorrhagic tendencies, in some cases, the patients recovered. In this article the terms agranulocytosis and agranulocytic angina are used interchangeably for the Schultz syndrome specifically and the general term granulocytopenia is used to include atypical and related cases.

Eight cases of granulocytopenia are presented, four of which seem to be agranulocytic angina. These cases are interesting because in several studies of the blood were made before the onset of the major illness, and because four of the eight patients recovered.

Lauter⁴ was the first to report a recovery. Four authors, including Moore and Wieder,⁵ Friedemann,⁶ McAlpin⁷ and Hutcheson,⁸ reported

¹ Submitted for publication, Aug 18, 1930

² From the Wilber E. Post Service of the Presbyterian Hospital

1 Schultz, W., and Verse. Ueber eigenartige Halserkrankungen (a) Monocyten Angina (b) Gangränisierende Prozesse und Defekt des Granulozytensystems, *Deutsche med Wchnschr* **48** 1495 (Nov 3) 1922

2 Turk, W. Septische Erkrankungen bei Verkümmern des Granulozytensystems, *Wien klin Wchnschr* **20** 157 (Feb 7) 1907

3 Kastlin, G. J. Agranulocytic Angina, *Am J M Sc* **173** 799 (June) 1927

4 Lauter. Zur Frage der mit Agranulozytose einhergehenden Fälle von septischer Angina, *Med Klin* **20** 1324 (Sept 21) 1924

5 Moore, J. A., and Wieder, H. S. Agranulocytic Angina. Report of a Case with Two Attacks, *I A M A* **85** 512 (Aug 15) 1925

6 Friedmann, U. Heilung der Angina agranulocytica durch Roentgenstrahlen, *Deutsche med Wchnschr* **53** 2193, 1927, *Ztschr f klin Med* **108** 54, 1928

7 McAlpin, K. Meeting of the Medical Society of the County of New York, March 26, 1928

8 Hutcheson, J. M. Agranulocytosis. Report of Five Cases, *Ann Int Med* **3** 883 (March) 1930

instances of recovery from the first attack and a fatal second attack. The patients were of both sexes, the interval between the attacks varied from three months to two years, and in the interval the polymorphonuclear neutrophilic leukocytes rose to 60 per cent and the white cells to 16,000. Windham⁹ reported recovery of a man, aged 34, Hutcheson⁸ of a woman, aged 66, Schultz¹⁰ of a woman, aged 30, Ordway and Gorham¹¹ of a woman, aged 46, and Blanton¹² of a man, aged 60, who was given 50 cc of leukocytic extract a day. Von Horvath,¹³ Stockinger,¹⁴ Wyatt,¹⁵ Finnigan¹⁶ and von Domarus¹⁷ reported recoveries. Mouquin and Fleury,¹⁸ Rosler¹⁹ and Spengler²⁰ each reported two recoveries. Zikowsky²¹ reported two cases in which recoveries were obtained with polyvalent streptococcus antitoxin. Friedemann⁶ reported four recoveries following roentgenotherapy, and Call, Gray and Hodges²² reported the recovery of a woman, aged 27, as a result of roentgen therapy. One of Thompson's²³ seven cases is probably a true agranulo-

9 Windham, R. E. Two Cases of Agranulocytic Angina, One Death and One Recovery, *Ann Otol, Rhin & Laryng* **38** 470 (June) 1929.

10 Schultz, W. Zur Frage der Anginen von atypischen Verlauf, *Deutsche med Wchnschr* **53** 1213 (July 15) 1927.

11 Ordway, Thomas, and Gorham, L. W. *Oxford Monographs. The Diagnosis and Treatment of Diseases of the Blood*, New York, Oxford University Press, 1930, vol. 9.

12 Blanton, W. B. Agranulocytic Angina with Recovery, *J. A. M. A.* **92** 2099 (June 22) 1929.

13 von Horvath, L. Case of Agranulocytic Angina Complicated by Gangrene of the Lung, *Folia haemat* **36** 352 (July) 1928.

14 Stockinger, W. Changes Taking Place in Blood Picture During Cure of Agranulocytosis, *Ztschr f d ges exper Med* **65** 27, 1929.

15 Wyatt, T. C. Case of Agranulocytic Angina with Recovery, *New England J Med* **199** 525 (Sept 13) 1928.

16 Finnigan, F. R. Agranulocytic Angina, *J. Missouri M. A.* **24** 258 (June) 1927.

17 von Domarus, A. Zur Lehre von der Agranulozytose, *Klin Wchnschr* **8** 779 (April 23) 1929.

18 Mouquin and Fleury. Agranulocytic Angina in Two Syphilitics, Recovery Following Treatment, *Bull et mem Soc med d hôp de Paris* **53** 693 (June 10) 1929.

19 Rosler, O. Agranulocytic Angina, *Wien med Wchnschr* **77** 603 (May 7) 1927.

20 Spengler, G. Zur Prognose der Agranulozytose, *Wien klin Wchnschr* **43** 45 (Jan 9) 1930.

21 Zikowsky, J. Zur Frage der Agranulozytose, *Wien klin Wchnschr* **40** 1376 (Nov 3) 1927, **40** 1420 (Nov 10) 1927.

22 Call, M., Gray, B. H., and Hodges, F. M. A Case of Agranulocytic Angina with Recovery, *Am J Roentgenol* **20** 550 (Dec) 1928.

23 Thompson, W. P. Leukopenia Resembling Agranulocytosis with Recovery, *Am J M Sc* **180** 232 (Aug) 1930.

cytosis in which recovery occurred Zadek²⁴ and Kohn²⁵ each reported a recovery in cases in which the diagnosis was uncertain, in one case the polymorphonuclears remained above 22 per cent and in the other 74 per cent of monocytes was present At least twenty-four recoveries have been reported in the literature

In at least three cases the disease developed while the patients were in a hospital for some other disease, including unexplained jaundice, tuberculous arthritis and fracture of the tibia in the cases of Ehrmann and Preuss,²⁶ Bantz²⁷ and Hunter,²⁸ respectively In all of these patients the blood count and differential count were normal on entrance Dwyer and Helwig²⁹ reported the case of a boy, aged 6, in whom a blood count showed white cells, 5,700, polymorphonuclears, 29 per cent, and lymphocytes, 65 per cent, seven weeks before the development of ulcers in the mouth Talley and Griffith³⁰ reported the case of a patient whose blood count showed 7,000 white cells, 31 per cent polymorphonuclears and 69 per cent lymphocytes one month before the onset of the disease One of Hutcheson's⁸ patients had an enlarged spleen and granulocytopenia five days before the onset of fever Ashworth and Maphis³¹ reported a white cell count of 3,500 six weeks before the onset of a fatal attack One of Potts' ³² patients, a hospital technician, had several blood counts made before her fatal illness fifteen months before the onset examination of the blood showed white cells, 6,000, lymphocytes, 70 per cent, eleven months before, the blood count showed white cells, 8,000, lymphocytes, 60 per cent, five months before, white cells, 12,000, lymphocytes 70 per cent Another of Potts' patients also showed a relative increase in lymphocytes before the fatal illness At least six cases in which the blood was abnormal before the onset of the fatal illness have been reported in the literature

24 Zadek, I Zur Frage der "Agranulozytose," *Med Klin* **21** 688 1925

25 Kohn, F Ueber monozytare Reaktion, *Wien Arch f inn Med* **7** 123 (Oct 20) 1923

26 Ehrmann, R, and Preuss, J Ueber Leukopenie und Schwund der Granulocyten bei Sepsis, *Klin Wchnschr* **4** 267, 1925

27 Bantz, R Beitrag zur Frage der "Agranulozytoses," *Munchen med Wchnschr* **72** 1200, 1925

28 Hunter, R J Agranulocytic Angina Report of a Case with Fracture of the Tibia, *Laryngoscope* **36** 348, 1926

29 Dwyer, H L, and Helwig, F C Agranulocytic Angina, *Am J Dis Child* **35** 1041 (June) 1928

30 Talley, J E, and Griffith, G C A Discussion of Six Cases of Agranulocytosis, *M Clin North America* **13** 1079 (Jan) 1930

31 Ashworth, O O, and Maphis, E C *Virginia M Monthly* **54** 237, 1927

32 Potts, J B Angina Agranulocytosis, *Arch Otolaryng* **9** 256 (March) 1929

REPORT OF CASES

CASE 1—Dr G S, a man, aged 33, single, was admitted to the Presbyterian Hospital on Aug 11, 1925, with a severe sore throat of three weeks' duration. The past history included a tonsillectomy in 1920. At that time *Streptococcus viridans* had been found in an abscess in one tonsil, the red cells numbered 4,200,000, and the white cells, 11,500. No differential count was made. On July 18, 1925, he had been treated for an ethmoid infection with cocaine and suction. He went on a motor trip, and a week later had a sore throat and a temperature of 103 F, and was given 5,000 units of diphtheria antitoxin even though cultures were negative for Klebs-Löffler's bacilli. A smear contained many fusiform bacilli, but no spirochetes, and he was given two doses of neoarsphenamine and one of arsphenamine. After five days in bed, he returned to work for a week.

Physical Examination—The patient seemed acutely ill and spoke with difficulty. There was no jaundice, and there were no petechiae. The nasopharynx was inflamed and covered with a thick whitish discharge. The anterior and posterior tonsillar pillars were swollen, and the whole neck was involved in a woody swelling that extended from the mandible to the sternum. There was tenderness and redness, but no localized fluctuation. The pupils, ears, nose, chest and abdomen were normal. The temperature was 101.4 F, the pulse rate, 110, the respiratory rate, 22, and the blood pressure, 105 systolic and 48 diastolic.

Laboratory Studies—The urine was normal, except for a trace of albumin. A culture of the blood was sterile. Smears from the throat contained gram-positive diplococci and occasional spirochetes and fusiform bacilli. The blood count showed red cells, 5,380,000, hemoglobin, 82 per cent, and white cells, 3,000, 2,800, 1,800, 600, 350 and 250 on successive days. A smear contained 51 per cent polymorphonuclears, 36 per cent lymphocytes, 8 per cent basket cells and 5 per cent myelocytes.

Course—The temperature rose about 1 F each day, and on August 16, five days after entrance, the patient died. At that time he was delirious and cyanotic. There were no râles, but the breath sounds were abnormal, and the temperature was 105.6 F, the pulse rate, 146, and the respiratory rate, 26. Treatment included two transfusions of 400 cc each of whole blood and 20 cc of Dick streptococcus antitoxin injected intramuscularly.

Postmortem Observations—The anatomic diagnosis was ulcerative stomatitis and pharyngitis, suppurating phlegmon of the neck, extensive bilateral bronchopneumonia, bilateral fibrinous pleuritis, acute general passive hyperemia, cloudy swelling of the kidneys, liver and pancreas, acute hyperplasia of the spleen, slight generalized jaundice, acute emaciation, and fibrous adhesions between the gall-bladder and the transverse mesocolon. There were practically no polymorphonuclears in the pneumonic portions of the lungs. In the bone-marrow there were many red cells, no polymorphonuclears, many lymphocytes, a normal number of megakaryocytes, a few myelocytes and some eosinophils. The intestinal tract was intact below the pharynx.

CASE 2—G K, a man, aged 39, married, with three healthy children, a laborer in a gasoline refinery, was admitted to the Presbyterian Hospital on Aug 12, 1926, with a sore jaw of two weeks' duration. He was born in Czechoslovakia and had been living in the United States for eight years. The past history was unimportant, except for a possible attack of tertian malaria in 1918, and influenza that made him ill for four months in 1920. The present illness began two weeks

before admission to the hospital, following the extraction of a left lower molar tooth. Swelling of the left side of the face, chills once or twice a day, severe headache, pain on mastication and soreness of the jaw developed within a few days.

Physical Examination—The patient appeared acutely ill and exhausted, and there were reddish papules on the chest suggestive of petechiae. There was an abscess behind the left ear that was later drained and *Staphylococcus aureus-hemolyticus* obtained. There was an offensive odor to the breath like that of decayed meat. In the mouth were numerous grayish-white areas about the gums and on the hard palate. There were marked pyorrhea, the pus exuding from a ragged wound in the lower jaw, enlargement and tenderness of the cervical lymph nodes and palpable but not greatly enlarged axillary, right epitrochlear and inguinal lymph nodes. The chest was normal, the abdomen soft and the spleen not palpable, the temperature was 103 F, the pulse rate, 84, the respiratory rate, 20 and the blood pressure, 110 systolic and 70 diastolic.

Laboratory Studies—The urine was normal, and the Wasseimann reaction was negative. In smears taken from the mouth many *Spnilla* and fusiform bacilli were found. Cultures contained *Streptococcus viridans*, gram-negative and gram-positive cocci and gram-negative bacilli. Two cultures of the blood and inoculations of the patient's blood into animals gave negative results. On admission, examination of the blood showed 4,400,000 red cells, 4,200 white cells, 5 per cent polymorphonuclears, 35 per cent lymphocytes and 60 per cent monocytes. Four days later, there were 2,400 white cells and 100 per cent lymphocytes. Subsequently, by August 22, the white cells had fallen steadily to 840, and a long search of a stained smear failed to reveal a single polymorphonuclear cell.

Course—The temperature fluctuated between 101 and 105 F during the seventeen days that the patient was in the hospital. A slight jaundice of the skin appeared on August 23. No hemorrhagic tendencies were noted. On August 29, the temperature rose to 103 F (rectal), the pulse rate to 124 and the respiratory rate to 38, there were rales in the chest, and the patient died. Treatment included gargles of peroxide, mouth washes and two intravenous injections of neoarsphenamine. A diagnosis of agranulocytic angina was made.

Postmortem Observations—The anatomic diagnosis was acute ulcerative pharyngitis, colitis and ileitis, hyperplasia of the upper anterior cervical lymph glands, embolic abscesses of the lungs, gangrene of the lower lobe of the left lung, bilateral serofibrinous pleuritis, marked hyperemia of the lungs, acute emaciation, and fibrous perisplenitis. No polymorphonuclears were present in the ulcers, but there were a few in a thrombus in one of the arterioles of the intestinal wall. The bone-marrow contained few cells, among which were red cells, megakaryocytes, normoblasts and lymphocytes, there were no polymorphonuclears.

CASE 3—L. H., a girl, aged 2, entered the Presbyterian Hospital on June 11, 1929, with a sore throat, inanition, lassitude and fever of one week's duration. The patient had had whooping cough before the age of 1 year, and she had been slightly pale for five weeks before the onset of the present illness. During the week before entering the hospital, the maximum daily temperature varied from 101 to 104.6 F (rectal).

Physical Examination—The patient was feverish, pale and fretful. The chest, abdomen, eyes, nose and ears were normal. The pharynx was red, and the tonsils were enlarged and covered with a grayish exudate. The cervical lymph nodes were enlarged and tender, but there was no marked enlargement of the glands in the axilla or groin.

Laboratory Studies—The urine contained a trace of albumin and many pus cells. The stools were normal, and the Wassermann and Kahn tests gave negative results. The coagulation time was nine minutes, the platelet count was 90,000, the van den Bergh test gave an immediate direct reaction, the icteric index was 70.9, and a fragility test did not show complete hemolysis in any tube from 0.50 to 0.24 per cent of sodium chloride. In the control, hemolysis started at 0.42 per cent and was complete at 0.32 per cent. The red cells varied from 890,000 to 2,600,000, and the hemoglobin from 24 to 45 per cent, the white cells numbered 3,600, 1,800, 1,800, 1,600, 1,500, 850, 1,200, 1,200, 2,100, 1,900, 7,200, 11,500 and 9,200 on different days. On June 12, there were 8 per cent polymorphonuclears (young forms), 88 per cent lymphocytes and 4 per cent monocytes. On July 6, there were 43 per cent polymorphonuclears, 47 per cent lymphocytes, 4 per cent monocytes and 6 per cent unclassified cells.

Course—The patient received three intraperitoneal transfusions of 400 cc of whole blood, and afterward became jaundiced. Treatment also included the administration of epinephrine intramuscularly and 20 cc of Squibb's leukocytic extract intramuscularly every four hours for eight days. The temperature remained between 102 and 105 F constantly for twelve days and gradually dropped to normal in the next four days. The patient was discharged in good condition on July 6.

Subsequent Course—For eight weeks the patient was well, then for four weeks she had a rise in temperature to 103 or 104 F almost every day. She reentered the hospital on October 30, with swollen glands of the neck, a soft systolic murmur over the precordium and pain and tenderness over the right tibia. Drill holes were made in the tibia, and it is not certain whether pus came out, but cultures were sterile. The temperature fluctuated between 99.4 and 106.6 F. A tentative clinical diagnosis of osteomyelitis and septicemia was confirmed by doubtful roentgen observations. The red cells and hemoglobin were as before, and the white cells varied from 11,500 to 24,000. Smears showed 2 per cent polymorphonuclears and 98 per cent lymphocytes (many immature). Death occurred on November 6. Autopsy was not performed.

CASE 4—B. B., a business man, aged 64, married, was admitted to the Presbyterian Hospital on June 25, 1929, with a swollen, painful jaw. In 1909, both arms and both legs were broken. He had not been feeling well for several months, and had been receiving arsenic for anemia. One week before entrance he had had an abscessed tooth removed. His jaw swelled the next day, and he had a temperature of from 102 to 103 F.

Physical Examination—There were no abnormalities, except in the mouth. There was no jaundice. There were two gangrenous patches on the gums and some edema of the appositioned cheek. The temperature was 103.6 F, the pulse rate, 112, the respiratory rate, 24 and the blood pressure, 131 systolic and 72 diastolic.

Laboratory Studies—The urine was normal, except for a trace of albumin. Spirochetes and fusiform bacilli were found in the gums. Material from an incision of the face over the jaw contained *Streptococcus viridans*, fusiform bacilli and spirochetes. Examination of the blood showed hemoglobin, 62 per cent, red cells, 3,400,000, white cells, 1,400 on entrance, 1,300, 1,150, 950, 850, 900 and 3,000 on successive days, 5,400 on July 4 and 5,200 on July 18. On July 1, with 3,000 white cells, there were 11 per cent polymorphonuclears, 58 per cent lymphocytes, 13 per cent monocytes, 16 per cent young polymorphonuclears and 2 per cent eosinophils.

Course—The temperature ranged from 101 to 105 F for eight days, and then suddenly became normal after a perineal abscess was opened. Tissue from this abscess contained round cells, but no polymorphonuclears. A thrombophlebitis of the right leg later developed. No hemorrhagic tendencies were noted. The patient was discharged in good condition on July 24, and a diagnosis of gangrene and subperiosteal abscess of the lower jaw, agranulocytic angina, rectal abscess and thrombophlebitis was made. Treatment included a transfusion of 500 cc of whole blood on June 27, and a mouth wash of 50 per cent hydrogen dioxide. The patient has been observed at intervals since leaving the hospital, and on July 1, 1930, the hemoglobin was 78 per cent, the red cells numbered more than 3,000,000, the white cells numbered 4,700, the differential count was normal, and the patient's general condition was excellent.

CASE 5—L. P., a woman, aged 37, unmarried, a school teacher, entered the Presbyterian Hospital on Oct. 26, 1929, with diarrhea, nausea, chills and fever, headache and soreness of the tongue of two days' duration. She had been in the hospital two months before with a condition diagnosed as spinal arthritis and secondary anemia. At that time examination of the blood showed red cells, 4,300,000; white cells, 6,100; the differential count was normal, with 65 per cent polymorphonuclears.

Physical Examination—There was no jaundice and no petechiae, and the examination was essentially negative except for a soft systolic murmur and inflamed tonsils.

Laboratory Studies—The urine, stools, results of cystoscopy and roentgen studies of the chest, colon and gallbladder were normal. An agglutination test for *B. melitensis* gave negative results. The red cells numbered 5,200,000, and on October 28, the differential count was normal, with 60 per cent polymorphonuclears. The white cells numbered 6,150 on October 26, 7,850 on November 3, 8,950 on November 10 at 4 p. m. and 1,375 at 9 p. m., and 675 on November 13.

Course—The patient had no more chills and only an occasional rise in temperature to 99.5 F during the first sixteen days in the hospital. On November 10, the tonsils became very sore, and the temperature rose to 103.6 F in twelve hours and remained elevated until death occurred on November 15. No smears were made after the fall in white cells. A diagnosis of acute follicular tonsillitis and lobar pneumonia was made. Autopsy was not performed.

CASE 6—M. R., a man, aged 20, single, a machinist in a brassworks, who was born in Italy, was admitted to the Presbyterian Hospital on June 14, 1930, with weakness and pallor of some months' duration, the condition had been worse for two weeks, and sore throat, headaches and dysphagia had been present for five days. Three days before admission a right peritonsillar abscess was incised by an outside physician. A thick yellowish discharge and profuse bleeding that lasted for ten hours resulted.

Physical Examination—There was pallor, but no jaundice or petechiae. There was much swelling of the right side of the pharynx, with a dirty gray, tenacious membrane, surrounded by a black border on the right tonsil. The breath smelled like decayed meat. There were coarse râles at the bases of both lungs, they soon disappeared. The heart and abdomen were normal. The temperature was 103.6 F, the pulse rate, 120, and the respiratory rate, 20.

Laboratory Studies—The urine and stools were normal. The Wassermann and Kahn tests gave negative results. There were *Sp. m.* and fusiform bacilli in smears from the raw area. The clotting time was one minute, the bleeding time,

seventeen minutes and the platelet count, 63,000. Twenty-six blood counts were made, the red cells varying from 980,000 to 4,100,000, and the hemoglobin from 24 to 62 per cent. Four times the white cells were below 1,000, being 900 on June 21, 24 and 25, and 940 on June 26. On June 21 and 24, there were 100 per cent lymphocytes, and long search of a stained smear failed to reveal a single polymorphonuclear cell. The highest point reached by the polymorphonuclear count was 31 per cent, on July 21. The last count, made on July 25, showed hemoglobin, 46 per cent, red cells, 2,540,000, white cells, 4,250, polymorphonuclears, 20 per cent, and lymphocytes, 80 per cent.

Course—The temperature followed a septic course, rising to 105 F. once the first week and to 102 or 103 F. at least once a week thereafter. After one of the blood transfusions, small petechial hemorrhages appeared on the chest, neck, shoulders, arms and legs. Nosebleeds occurred several times, and the edges of the incisions made to expose the veins for transfusion healed with difficulty. A thrombophlebitis followed one of these incisions on the dorsum of the right foot. The treatment included ten transfusions of blood of 500 cc. each, six ampules of liver extract no. 343 a day, mass of ferrous carbonate, 10 per cent neosarsphenamine in glycerin locally and sedatives. When last seen, the patient was still in the hospital and was to leave when the thrombophlebitis was better. His general condition was better, and his throat had practically healed. A diagnosis of agranulocytic angina was made.

CASE 7—M. H., a woman, aged 23, single, a nurse, entered the Presbyterian Hospital on June 17, 1930, with the complaint of fever, sore throat, nausea and vomiting of two days' duration. A tonsillectomy and thyroidectomy had been performed in 1923. The patient was in the hospital in 1928, with colitis and malnutrition, at that time, examination of the blood showed hemoglobin, 74 per cent, red cells, 3,870,000, and white cells, 6,500, no differential count was made. The onset of the present illness was sudden, being accompanied by a chill.

Physical Examination—The patient was weak and exhausted. The throat was red and swollen. There was a whitish membrane in the right tonsillar fossa and about the right tonsillar pillar. The cervical lymph glands were swollen and tender. The eyes, ears, chest and abdomen were normal, and the spleen was not palpable. The temperature was 101.4 F., the pulse rate 100, the respiratory rate, 20 and the blood pressure, 102 systolic and 64 diastolic.

Laboratory Studies—The urine contained a trace of albumin, but was otherwise normal. Chemical analysis of the stools and blood (including urea, uric acid, creatinine, total nonprotein nitrogen, sugar and chlorides) gave normal results. Smears from the throat revealed no spirochetes or fusiform bacilli. Wassermann and Kahn tests gave negative results. Careful hematologic studies were made by Dr. P. H. Herron. A platelet count and the bleeding time were normal. On the day of admission, the average of seven white counts was 1,000, red cells, 4,300,000, hemoglobin, 86 per cent (Newcomber), and the differential count showed 1 per cent polymorphonuclears, 96 per cent lymphocytes and 3 per cent lymphoblasts.

Course—During the patient's stay in the hospital, thirty-eight white cell counts were made, four of which gave a figure below 1,000, the lowest being 725 on June 18. The next day 500 cc. of whole blood was given by direct transfusion. In four days the white cells numbered 9,480 (the highest point reached) and the membrane in the throat disappeared. That evening an abscess in the neck was opened, and the white cells fell to 4,850 the next day. The temperature varied

from 99 to 101 F for eight days and thereafter was normal. The white count fluctuated between 3,500 and 5,000 from June 24 to July 13, when the patient was discharged in good condition. Treatment included the single transfusion of blood, the incision of the abscess in the neck and four ampules of liver extract no 343 a day. Subsequent examinations showed the white cells between 6,000 and 8,000, and the patient in good condition. On July 28, 1930, there were 67 per cent polymorphonuclears and 33 per cent lymphocytes.

CASE 8—A K, a man, single, a medical student, aged 31, was admitted to the Presbyterian Hospital on the Wilber E. Post service on June 21, 1930, with an acutely sore throat and general malaise of one day's duration. The patient had had measles and diphtheria in Russia in 1905, and arthritis in 1929. He was in the hospital from April 7 to April 12, 1930, with a febrile attack. Pneumococci and *Streptococcus viridans* were found in the throat, and the white cells numbered 16,000. On May 1, examination of the blood showed red cells, 5,000,000, white cells, 5,500, and 29 per cent polymorphonuclears, 63 per cent lymphocytes, 4 per cent monocytes, 0.5 per cent basophils, 0.5 per cent eosinophils, 2.5 per cent metamyelocytes and 0.5 per cent myelocytes (?). On June 13, a tonsillectomy was performed. The next week the patient was well and served as a clinical clerk in the hospital. He did not come in contact with the patients in cases 6 and 7. The present illness began June 20, with a sudden onset, but no chill, severe headache, severe diffuse discomfort in the extremities, weakness, sore throat, dizziness and fever.

Physical Examination—The patient was quite weak. There were no petechiae, and there was no jaundice. The pharynx was not red, and there was no post-nasal discharge. There was a well defined whitish membrane in both tonsillar fossae. The upper and lower anterior cervical lymph glands were enlarged and slightly tender. The pupils, sclerae, nose, ears, sinuses, teeth, gums, lungs, heart, cardiohepatic angle and abdomen were normal. There was no edema, and the spleen was not palpable. The inguinal and posterior cervical glands were barely palpable, and the axillary and epitrochlear glands were not palpable. The temperature was 102.8 F, the pulse rate, 104, the respiratory rate, 20, and the blood pressure, 118 systolic and 74 diastolic.

Laboratory Studies—The urine was normal, except for a trace of albumin in three of seven samples. The stools were normal. Wassermann and Kahn tests gave negative results. On June 23, smears from the throat contained cocci, *Spnilla* and fusiform bacilli, and on June 29, no *Spnilla*, occasional fusiform bacilli, many encapsulated diplococci and several perfect polymorphonuclears. On June 23, *Staphylococcus albus* and *Streptococcus hemolyticus* were grown from cultures taken from the throat, and on June 29, *Streptococcus hemolyticus* and *Streptococcus viridans*. No Klebs-Löffler's bacilli or *B. pyocyaneus* were found. In cultures of the blood taken on June 22, two hemolytic colonies described as gram-positive cocci were grown. They did not grow when subcultivated, and were not further identified. The clotting time was one and a fourth minutes and the bleeding time three and a fourth minutes, and the platelets numbered 160,000. A corpuscle fragility test showed beginning hemolysis at 0.40 per cent sodium chloride, and complete hemolysis at 0.36 per cent, a control showed 0.42 and 0.36 per cent, respectively. A Widal test showed positive agglutination for *B. typhosus* and *B. paratyphosus* A and B at a dilution of 1:160, and no agglutination for *B. melitensis*, bovine *B. abortus* and porcine *B. abortus*. The patient had undergone antityphoid vaccination in 1915 and in the spring of 1929. A

record of the blood counts is shown in table 1. It is seen that to some extent there is what Arneith calls a shift to the left and also what Schilling terms a degenerative shift. The changes in the lymphocytes that I have called degeneration consisted essentially in vacuolization of the cytoplasm.

Course—The patient had a septic temperature for four days, with the highest peak, 103.4 F., on the second day. There was no fever after June 24. There were vomiting, a severe headache that required morphine, difficulty in opening the mouth and in swallowing, herpes simplex on the lip that soon disappeared and cyanosis of the mucous membranes that developed on June 24 and persisted.

TABLE 1—*Hemogram of Changes in the Blood in Case 8 (A Modified Form of the Schilling Hemogram)*

Date, 1930	Hemoglobin	Erythrocytes	Total Leukocytes	Neutrophils							Lymphocytes	Monocytes	Degenerated Lymphocytes
				Basophils	Eosinophils	Myelocytes	Juvenile Forms	Stab nucleated Forms	Segment nucleated Forms (Mature Polymorphonuclears)				
June 21	86	5,070,000	2,300										
June 22			1,900	0	0	0	1	0.6	0	93.4	5	0	
June 23			3,100	0	0	1	5	4.0	0	82.0	8	0	
June 23			3,700	0	0	2	2	5.0	0	83.0	8	0	
June 24			3,600										
June 24	90		4,600										
June 25			4,400	0	0	0	2	3.0	8	79.0	8	—	
June 25		4,870,000	5,000										
June 26			4,100	0	0	0	2	2.0	12	80.0	4	—	+
June 27	95	4,790,000	5,750	1	0	0	1	13.0	14	69.0	2	—	+
June 28			10,000	0	0	0	4	14.0	22	57.0	3	—	+
June 29			10,500										
June 30			11,100	0	0	0	2	10.0	31	55.0	4	—	+
July 1			9,800										
July 3			6,200										
July 8	92	4,910,000	9,900	0	0.5	0	3	5.0	39	50.5	2	—	+
July 14			5,500	0	0	1	2	4.0	43	53.0	2	—	+
July 29			5,700	0	0	0	1	4.0	18	72.0	5	—	+
Aug 9	101	5,200,000	7,000	0	0	0	0	4.0	50	44.0	2	0	

The patient was discharged on July 2 in good condition and has been seen at weekly intervals since. The general treatment included rest and the administration of fluids and sedatives. Attempts at specific treatment included two ampules of liver extract no. 343 a day, the application of mass of ferrous carbonate and two intravenous injections of neoarsphenamine 0.45 Gm. on June 22 and 0.3 Gm. on June 25. Local treatment included applications of 10 per cent neoarsphenamine in glycerin and gargles of saturated solution of sodium perborate, 1,200 potassium permanganate and 50 per cent solution of hydrogen dioxide used alternately.

COMMENT

The question arises as to how many of these cases are true agranulocytic angina. In agranulocytic angina the bone-marrow element producing the polymorphonuclear neutrophilic leukocytes is interfered with, and the elements producing red cells and platelets are undisturbed. In

all of Schultz' original cases, discussed by his pupil Leon,³³ the red cells, hemoglobin and platelets were normal, and there were no hemorrhagic tendencies. This qualification tends to rule out cases 3 and 6. These two cases, as well as many reported in the literature as agranulocytic angina, are probably of a type similar to aplastic anemia. In this condition all three of the bone-marrow elements are injured. In cases 1 and 5 there were incomplete blood counts. Two physicians in attendance on the patient in case 1 stated in a personal communication that the differential count included in the history is in error, and that several other smears not recorded contained almost no polymorphonuclears. In

TABLE 2—Summary of Observations on the Eight Cases Reported

	Agranulocytic Angina				Average or Total	Granulocytopenia				Average or Total	Grand Total
	Case 2	Case 4	Case 7	Case 8		Case 1	Case 3	Case 5	Case 6		
Age	39	64	23	31	39	33	2	37	20	23	31
Sex	M	M	F	M	1F	M	F	F	M	2F	3F
Vincent's organisms	+	+	0	+	3	+			+	2	5
Streptococcus viridans	+	+	+	+	4	+				1	5
Icterus	+	0	0	0	1	+	+	0	0	2	3
Involvement of throat	+	+	+	+	4	+	+	+	+	4	8
Throat ulcerated	+	+	+	+	4	+	0	0	+	2	6
Albumin in urine	0	+	+	+	3	+	+	0	0	2	5
Enlarged glands	+	+	+	+	3	+	+		+	3	6
Anemia	0	+	0	0	1	0	++	0	++	2	3
Hemorrhagic tendency	0	0	0	0	0	0	+	0	+	2	2
Lowest white count	840	850	900	1,900	1,120	250	850	675	900	670	890
Lowest polymorphonuclears, %	0.0	11.0	1.0	0.6	3.0	?	2.0		0.0	1.0	2.0
Blood culture	Neg			?	Neg	Neg	Neg	+	+	Neg	Neg
Treatment by											
Surgical intervention	+	+	+	0	3	0	+	0	+	2	5
Transfusion	0	1	1	0	2	2	3	0	10	3	5
Arsenic	+	+	0	+	3	+	0	0	+	2	5
Leukocytic extract	0	0	0	0	4	0	+	0	0	1	1
Dick serum	0	0	0	0	0	+	0	0	0	1	1
Liver extract	0	0	+	+	2	0	0	0	+	1	3
Recovery	0	+	+	+	3	0	0	0	+	1	4

case 5 no differential count was made after the drop in white cells. In these two cases there was also sepsis, which, according to Leon,³³ puts them in another group. I consider the other four cases, in three of which the patients recovered, to be agranulocytic angina. It is seen that this division is somewhat arbitrary.

In 2 of the cases the condition developed after the extraction of a tooth. Hill³⁴ reported 4 such cases. A summary of observations in the 8 new cases reported is given in table 2. In general, the different items are similar to those previously reported in other cases. The preponderance in males, the frequency of finding *Streptococcus viridans* in

33 Leon, A. Ueber gangranisierende Prozesse mit Defekt des Granulozytensystems ("Agranulozytosen"), *Deutsches Arch f klin Med* **143** 118, 1923.

34 Hill, H. P. Acute Leukemia and Agranulocytic Angina Associated with or Following Removal of Teeth. Report of Four Cases, *California & West Med* **25** 609 (Nov.) 1926.

smears from the throat and abscesses of the throat and the frequent albuminuria are interesting. Three of the 4 recoveries occurred in cases that were probably agranulocytic angina. These 3, with the 24 reported in the literature in about 150 total cases, give a mortality of 82 per cent. Kastlin³ reported a mortality of 95 per cent in 43 cases reviewed, Friedemann⁶ 92 per cent in 47 cases and Ordway and Gorham¹¹ 89 per cent in 82 cases reviewed. The increasing use of blood counts will probably cause the reported mortality rate to continue to decrease.

In looking over the new cases and those reported in the literature, three somewhat related observations stand out: (1) the presence of ulcers in extra-oral mucous surfaces, as in case 2 and in the reports of Piette,³⁵ Petri³⁶ and Schultz,¹ (2) the occurrence of ulceration in some cases after granulocytopenia is present, and (3) the occurrence of oral ulcerations as a terminal manifestation in aplastic anemia and other conditions in which there is a granulocytopenia. This may indicate that one element in agranulocytic angina is a constitutional defect in the bone-marrow. In view of this possible defect of the bone-marrow it is of interest that one of my patients broke both legs and arms in 1909. One worked in a gasoline refinery and another in a brassworks, but it was not determined how much of a factor this might have been.

The treatment for agranulocytic angina is still uncertain. In my series the patients in the fatal cases received practically the same treatment as those who recovered. In five of the cases in which recovery is reported in the literature, the patient received roentgen therapy, this therapy was not used in the cases here reported. At least eight cases of agranulocytic angina have been ascribed to the arsenical treatment for syphilis, e. g., the cases of Pouzin and Malègue.³⁷ However, arsenic was used in the treatment for agranulocytic angina in five of the eight cases considered in this paper. In reviewing eighty-two cases, Ordway and Gorham¹¹ stated the belief that in general the patients in whom pus has been localized and drainage established are more apt to recover. In five of the eight new cases, there were localized abscesses that required surgical drainage, and in two of them the patients died. In two of the cases in which the patients recovered liver extract was used.

SUMMARY

1 Eight cases of granulocytopenia with four recoveries are presented.

2 In four of the eight cases the condition was possibly agranulocytic angina. Three of the patients recovered.

35 Piette, E. C. Histopathology of Agranulocytic Angina, *J. A. M. A.* **84** 1415 (May 9) 1925.

36 Petri, E. Intestinal Changes in Agranulocytosis, *Deutsche med. Wchnschr.* **50** 1017 (July 25) 1924.

37 Pouzin and Malègue. Case of Agranulocytic Angina Following Arsenical Treatment, *Bull. et mém. Soc. méd. d' hôp. de Paris* **52**:1786, 1928.

3 A mild granulocytopenia sometimes precedes the onset of agranulocytic angina

4 In four previously reported cases of agranulocytic angina, the patients died of a second attack

5 One element in agranulocytic angina may be a constitutional defect of the bone-marrow

6 Agranulocytic angina may be confused with aplastic anemia

7 Liver extract was used in two of the cases in which recovery occurred

8 At least 150 cases of agranulocytic angina with 27 recoveries have been reported to date The approximate reported mortality rate is 82 per cent

ADDENDUM

The patient in case 6 died on Oct 21, 1930, with a condition diagnosed aplastic anemia with secondary gangrenous stomatitis During the last two months of life the red cells numbered between 1,600,000 and 2,200,000, the white cells between 1,200 and 2,600, and the polymorphonuclears 12 per cent No autopsy was performed The patients in cases 7 and 8 are living and well, with almost normal blood In November, 1930, the latter patient, A K, gave 500 cc of blood to a patient, not included in this series, who was suffering from granulocytopenia with stomatitis The new patient recovered No previous instance in which this form of therapy was used in granulocytopenia could be found in the literature

Drs Gatewood, E McGinnis, L C Gatewood, F B Moorehead, R T Woodyatt, G L McWhorter and E E Irons gave me permission to discuss their cases, and Dr C W Apfelbach supplied the postmortem data

A TEST FOR GASTRIC ACIDITY

THE "COMBINED TEST"

M J MATZNER, M D

IRVING GRAY, M D

AND

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BROOKLYN

We recently discussed the advantages of the "combined test" in obtaining controlled results in determinations of gastric acidity. The combined test embodies the direct study of gastric acidity and the simultaneous estimation of the urinary reaction. This test is based on the observation that persons having a relatively normal gastric secretion are prone to develop a less acid urine after meals, commonly referred to as the alkaline tide. On the other hand, patients with a true achlorhydria tend to show a relative fixation of the urinary reaction.

In our previous investigations, we employed histamine subcutaneously as the gastric stimulant. The fact that no more than 50 per cent of our patients, in whom free hydrochloric acid was demonstrated in the gastric extractions after the subcutaneous injection of histamine, developed a definite urinary alkaline tide caused us to abandon the use of histamine as the gastric stimulant in the combined test.

We decided to use Steero bouillon cubes (one Steero cube in a cup of warm water) as the gastric stimulant. Steero bouillon lends itself readily to this purpose because of its ease of preparation and its effectiveness as a gastric stimulant.

METHOD OF PROCEDURE

The patient was requested to urinate at 6:30 a. m., emptying the bladder as completely as possible. This was done again at 8:30 a. m., and the hydrogen ion concentration (p_H) of this second specimen was determined immediately.

A Rehfuess tube was passed about 9:00 a. m. and the gastric contents of the stomach during fasting extracted. The stomach was washed with water until a clear return was obtained. The patient was then requested to drink two cups of warm Steero bouillon (one cube to a cup of warm water). Gastric extractions were made from every twenty to thirty minutes over a period of from three to five hours. The patient was instructed to empty the bladder as completely as possible at each urination, and was kept at comparative rest throughout the entire test. The gastric specimens were quantitatively analyzed for free and total acidity.

* Submitted for publication, Aug 11, 1930

The hydrogen ion concentration of the urine was immediately determined with the Hellige comparator¹. A determination can be made in a few minutes. This method is extremely simple and lends itself readily to clinical use.

RESULTS

Nineteen patients were studied in group 1. The test showed free hydrochloric acid in the gastric extractions, and a definite urinary alkaline tide was noted.

TABLE 1—Result of the "Combined Test" in Group 1

Number	Diagnosis	Maximum Gastric Acidity		pH of Urine	
		Free Hydrochloric Acid	Total Acidity	Initial pH	Maximum pH
1	Neurosis	21	37	7.4	8.1
2	Duodenal ulcer	47	63	5.6	7.0
3	Neurosis	44	61	5.0	6.0
4	Catarrhal jaundice	47	63	5.6	7.6
5	Chronic constipation	21	25	5.6	6.4
6	Gastric carcinoma	46	48	5.6	6.8
7	Duodenal ulcer	24	26	5.0	7.0
8	Gastric ulcer, syphilis	40	56	5.2	6.0
9	Duodenal ulcer, syphilis	60	64	6.4	7.6
10	Neurosis, postoperative adhesions	20	30	6.8	7.3
11	Duodenal ulcer	23	40	5.2	6.0
12	Chronic cholecystitis	30	34	6.2	7.2
13	Duodenal ulcer	40	50	6.4	7.6
14	Neurosis	15	22	5.2	6.4
15	Duodenal ulcer	40	60	5.2	6.8
16	Duodenal ulcer	40	60	6.0	6.8
17	Duodenal ulcer	60	64	5.2	7.2
18	Duodenal ulcer?	30	48	5.2	7.0
19	Duodenal ulcer?	51	59	4.8	5.7

TABLE 2—Result of the "Combined Test" in Group 2

Number	Diagnosis	Maximum Gastric Acidity		pH of Urine	
		Free Hydrochloric Acid	Total Acidity	Initial pH	Maximum pH
20	Duodenal ulcer, hypersecretion	86	90	7.6	7.6
21	Chronic constipation	30	40	6.2	6.2
22	Chronic cholecystitis	32	38	5.8	5.2

TABLE 3—Result of the "Combined Test" in Group 3

Number	Diagnosis	Maximum Gastric Acidity		pH of Urine	
		Free Hydrochloric Acid	Total Acidity	Initial pH	Maximum pH
23	Generalized arteriosclerosis	0	10	5.2	5.2
24	Pernicious anemia	0	8	6.0	5.2

Group 2 consisted of three patients in whom gastric extractions showed free hydrochloric acid and in whom no urinary alkaline tide was observed.

The two patients in group 3 demonstrated an achlorhydria and a relative fixation of the urinary reaction (no alkaline tide).

1 This apparatus may be obtained from Eimer and Amend, New York City.

COMMENT

The method employed in our "combined test" possesses many advantages. The Hellige comparator lends itself readily to clinical use in determinations of urinary p_H . It is simple, rapid and sufficiently accurate for this test.

The use of Steiro bouillon cubes as the gastric stimulant has proved satisfactory. The Steiro cubes can easily be obtained, and the test meal readily prepared. The content of meat extract in the cubes has proved sufficiently great to serve as an excellent gastric stimulant.

In our studies, three patients in whom we were able to demonstrate free hydrochloric acid in the gastric extractions failed to develop an alkaline tide. One of these patients (no 20) with a duodenal ulcer had a marked hypersecretion and hyperacidity (Reichman's disease). Kauders and Porges² observed that this group frequently does not develop an alkaline tide because of their continuous maximal gastric secretion. Other factors, such as impaired renal function, previous diet, etc., may be responsible for a lack of agreement between the gastric acidity and the change in urinary reaction.

CLINICAL APPLICATION

We feel that the direct study of the gastric contents is invaluable. However, in patients with cardiac disease and hypertension or in those unwilling to permit the passage of a tube, one can frequently gain information as to the presence or absence of free hydrochloric acid in the gastric content by a study of the urinary alkaline tide.

This test may prove of value in the study of gastric acidity in patients in whom marked duodenal or duodenojejunal regurgitation occurs. We are particularly interested in studying the group of patients who have undergone partial gastrectomies. We feel that many of these patients may be reported as "anacid," possibly erroneously so, because of the neutralization of the gastric contents by marked duodenojejunal regurgitation through a large stoma. The "combined test" may prove of value in deciding this question by the simultaneous study of the gastric contents and the urinary reaction.

CONCLUSIONS

1. A simple combined test for gastric acidity with Steiro bouillon cubes as the stimulant is described.
2. The gastric analysis and changes in urinary reaction (p_H) agreed in about 85 per cent of the patients studied.
3. The clinical application of the combined tests has been indicated.

²Kauders, F., Porges, O., and Essen, H. *Deutsche med. Wchnschr.* **47**: 1415 (Nov. 24) 1921.

THE TREATMENT OF RESPIRATORY ARREST IN THE DRINKER RESPIRATOR

A CLINICAL AND EXPERIMENTAL STUDY¹

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Failure of respiration is a decisive occurrence that must be met at once by substitution of mechanically induced breathing. It is so critical an emergency, so desperately certain to be fatal, that appliances and methods for artificial respiration have even been granted a certain margin of danger if they, in the main, promised to perform well. In his review of the history of artificial respiration, Keith¹ described the development of bellows appliances for resuscitation as early as 1732. Such devices were given much attention, and were not discarded for use by the Royal Humane Society until 1837. Their rejection resulted from the large amount of harm that it was shown they might produce. The lungmotor and the pulmotor, modern appliances very similar to the bellows devices of a hundred years ago, have had an identical history. The introduction of carbon dioxide as a stimulant for breathing in asphyxia in 1922 gave promise of doing away with the necessity for aids other than the simple positive pressure method of artificial respiration. But, though most gratifying results were obtained, cases kept appearing in which it seemed that life might have been saved had it been possible to provide artificial respiration for a long period of time by a method imitating normal breathing and permitting the patient to sleep and take food.

In 1929, Drinker and Shaw² published a description of a device capable of meeting these requirements. Since then many patients have been treated in this new respirator. Several of these cases have

¹ Submitted for publication, Aug. 30, 1930.

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¹ Keith, A. *Lancet* **1** 745, 1909.

² Drinker, P., and Shaw, L. A. *J. Clin. Investigation* **7** 229, 1929. Shaw, L. A., and Drinker, P. *J. Clin. Investigation* **8** 33, 1929.

been highly successful, of which two instances have been published³ and have indicated that patients may be made to breathe artificially over long periods without the slightest evidence of untoward effects from the artificial respiration. Many other cases have terminated fatally. This is to be expected when it is considered that the device has been used in the treatment for rapidly progressing poliomyelitis, advanced carbon monoxide poisoning, respiratory failure later ascertained to be due to cerebral hemorrhage, etc. Such results have nothing to do with the efficacy of the respirator. That question depends on the ability of the device to operate for long periods without of itself contributing damage to the lungs.

In using the respirator, the subject is enclosed in an airtight metal tank, from which the head protrudes through a rubber collar. Respiratory movements are induced by an electrically driven pump and an appropriate system of valves. While a partial vacuum is being produced around the body, the chest enlarges and inspiration occurs. Expiration results from the elastic recoil of the chest when the partial vacuum is abolished by the succeeding revolution of a valve. The rate of breathing is controlled by the rate of the motor and the depth of breathing by an increase or decrease of the severity of the suction applied inside the metal tank to the body of the subject.

Studies on normal persons and a realization of the conditions that are likely to be met clinically have raised three important questions in connection with the employment of this new method of artificial respiration. 1. What is the depth limit of artificial respiration (expressed in centimeters of water, negative pressure) that can be employed with safety? 2. Should signs of respiratory failure increase—in spite of moderate usage of the respirator—can the efficiency of the method be increased by increasing the negative pressure, or does one begin to produce damage to the lungs and so jeopardize the chance for recovery? 3. What special technic is necessary in order to apply this form of therapy to infants suffering from acute asphyxia?

Partial answers to these questions are available through experience with normal subjects, with patients and through experiments on animals. They indicate that the respirator is extraordinarily efficient in getting air into the lungs, except in the presence of atelectasis or gross bronchial obstruction. It is this very efficiency that makes it necessary that the

3. Wightman, H. D., and Shaughnessy, T. J. A Case of Respiratory Failure Successfully Treated in the Drinker Respirator, *J. A. M. A.* **93** 456 (Aug. 10) 1929. Shambaugh, G. E., Harrison, W. G., and Farrell, J. L. Treatment of the Respiratory Paralysis of Poliomyelitis in a Respiratory Chamber, *J. A. M. A.* **94** 1371 (May 3) 1930.

appliance be used with discernment and prudence, particularly in the presence of pathologic conditions in the lungs. The following fatal cases have been selected from our experience during the past year. In each instance the respirator was employed against great odds and as skillfully as our judgment permitted. It is doubtful whether today the outcome could have been altered in a single instance, but certain lessons were learned that help to answer the questions we have asked, and since the use of the respirator is increasing this experience may be of value to others. The cases reported occurred in two adults and six premature infants.

REPORT OF CASES

CASE 1—*Acute Poliomyelitis with a Terminal Bronchopneumonia*

L. C., a white woman, aged 25, was admitted to the Peter Bent Brigham Hospital on Oct. 16, 1929, suffering from respiratory difficulty and paralysis of the extremities. She became sick on October 11, with headache, fever, vomiting, stiffness of the neck and malaise, followed by a gradually increasing paralysis. Difficulty in breathing was observed the same day. At 1 00 a. m. on the day of admission (October 16), the pulse rate and respiratory rate were elevated, and the temperature was 104 F. The abdominal muscles were tense. There was a loss of power in the right arm. The knee jerks were gone, and both legs were paralyzed. The patient was cyanotic, and during examination became more so on being turned over. Her condition was diagnosed as poliomyelitis. She was placed in the respirator at 1 15 a. m., already suffering from lack of oxygen and able to breathe but slightly. At first a number of deep breaths were given, the negative pressure being raised to 35 cm. It was later reduced to 20 cm. Below this point the patient would object and ask for more air. The following day the pump was run at 25 cm. pressure and at a breathing rate of 20 per minute. While the patient was being given artificial respiration, the cyanosis and dyspnea disappeared. Both recurred rapidly whenever the machine was stopped. At the end of eight hours of treatment, swallowing became difficult, and the pump could not be stopped for more than a minute without the development of cyanosis. On the morning of October 17, the patient was unable to swallow. That evening, a negative pressure of 28 cm. was required in order to prevent the appearance of cyanosis. Death occurred at 4 00 a. m. on October 18.

On admission there were no marked signs of abnormality in the lungs as evidenced by loud râles or marked dulness. The breathing was, however, so bad as to preclude the possibility of careful examination. Near the time of death, bubbling râles could be heard above the noise of the respirator. During the entire illness, the condition was so critical as to make thorough examination of the chest impossible, so that there is no direct evidence on the development and progress of the condition of the lungs found at autopsy.

In summary, this was a rapidly advancing case of poliomyelitis, the patient was somewhat asphyxiated when treatment began and so severely paralyzed as to make it impossible to change her position during most of the fifty-five hours that she was in the respirator. An alarming increase in pulse rate began about twenty hours after admission, and possibly indicates the onset of pneumonia. The patient lay flat on her back in a horizontal, not a head-down, position, and for the last sixteen hours was made to breathe only by the use of excessively high suction.

Autopsy Report—The anterior mediastinum and pleural cavities showed nothing abnormal. The right lung weighed 370 Gm and the left 330 Gm. Both lungs were crepitant throughout, though the crepitation was diminished in degree in both lower lobes, particularly in the right. Along the most dependent margins of both lower lobes there was a fairly well demarcated dark reddish-blue region representing intense congestion, however, even here there was a slight amount of crepitation. The visceral pleurae were everywhere moist, smooth and glistening. The surfaces of the lungs were mottled gray and black and grayish yellow, tinged by red in the lower part of the lobe. Surfaces, made by cutting, were pink in the upper part of the lobes and red in the lower part, owing to the more intense congestion in the latter regions. Numerous small, blotchy red regions were noted throughout both lungs, representing early bronchopneumonia. In the lower part of the right lobe there were several consolidated regions, practically airless. On section, these showed deep red granular surfaces from which a moderate amount of serosanguineous and purulent material could be expressed on pressure. Sections through the most dependent portions of the lower parts of both lobes, the areas that appear deep reddish blue externally, were dark red and represented mainly intense congestion. Several branches of the pulmonary vessels were opened, and no ante mortem clots were found. Within the bronchi there was seen a small amount of mucoid material, and near the regions of consolidation, mucopurulent material. The bronchial walls were slightly injected.

Microscopic Examination—Two sections of lung showed an acute bronchopneumonia, hemorrhage, edema and congestion. The pneumonic process was of an acute type characterized by hemorrhage and a varying degree of polymorphonuclear infiltration. The hemorrhagic exudate, however, was the outstanding feature. The alveoli frequently contained round or oval clear spaces about which there was a rim of exudate. The clear spaces represented globules of entrapped air. In the exudate, both of hemorrhagic and of purulent type, there were many cocci, usually in chains. The bronchi contained an exudate more or less similar to that found in the alveoli. Their epithelium was degenerated, owing for the most part to postmortem changes, but there were some bronchioles that showed rather extensive infiltration by polymorphonuclear leukocytes. All of the blood vessels showed marked congestion, and some of the smaller ones thrombosis.

The type of hemorrhagic exudate observed is frequently found in acute streptococcic infections of the respiratory tract. That exudate entered bronchi and alveoli by an aspirational process was evident by the entrapped globules of air. It was the opinion of the pathologist that the hemorrhagic exudate in the alveoli might be an expression of trauma from the artificial respiration, although it was equally probable that it was a streptococcus effect, as streptococci were abundant in the exudate.

In this case the patient had suffered from acute asphyxia for about one hour prior to the use of the respirator. In conscious patients with poliomyelitis, with very complete respiratory paralysis, it has been found that the patients' feelings are the best guide to the volume of breathing to be provided by the respirator. Overventilation is always unpleasant. A normal person in the respirator will ask for an adjustment of rate and depth of breathing that avoids the production of apnea when the respirator is stopped. Paralyzed patients are capable of giving the same instruction, although the truth of their judgment cannot be proved by

stopping the machine. As the disease progressed in L. C., cyanosis again developed, and to combat this the suction applied by the respirator to produce inspiration was increased. It is our opinion that on admission—possibly as a result of asphyxia, for the type of asphyxia due to carbon monoxide poisoning is capable of producing fluid in the alveoli and bronchioles, and possibly as an independent process—this patient had excess fluid in the lungs, which, as she lay flat on her back, gravitated to the dependent posterior portions of the lungs and slowly shut off large areas from the entrance of air. To combat this the action of the respirator was increased, but the result of this increase was probably to pack bronchiolar exudate to a maximum degree and to produce hemorrhage from overinflation of such alveoli as were compelled to receive air or were open but shut off from the air by bronchiolar plugs. It has been our experience that patients known to have diffuse exudative processes in the lungs do poorly in the respirator, and maximally so if it is impossible to change their position fairly frequently. In a case as far advanced as that of L. C., the patient must be treated, but the respirator should never be run with more than minimal pressures, and the foot of the appliance should be raised to promote drainage toward the mouth, as indicated by the animal experiments that conclude the paper.

CASE 2—*Acute Poliomyelitis with Bronchopneumonia and with Traumatic Emphysema of the Lungs and Mediastinum*

H. P., a white man, aged 18, was admitted to the Peter Bent Brigham Hospital on Oct. 27, 1929, with the chief complaint of difficulty in breathing. For two weeks prior to admission the patient had been ill with a mucopurulent bronchitis. Forty-eight hours before admission, dizziness, fever and chilly sensations were observed. Twenty-four hours before admission paralysis began, the right arm becoming affected first. The morning of the day of admission, the accessory muscles of respiration were brought into play, and coughing became impossible. On admission the patient was extremely cyanotic. He was placed at once in the respirator, which promptly relieved the cyanosis, but did not restore consciousness. At this time a negative pressure of 20 cm. was employed with a respiratory rate of 20 per minute. The artificial respiration was begun at 12:50 a. m., October 27, and was carried on continuously until death at 3:35 p. m., October 28. From time to time large amounts of thick yellow mucus were raised, and four hours before death a foamy white mucus was observed. At this time swallowing became difficult. Although moderate negative pressures were employed most of the time, toward the end of life extremely high pressures were used (from 40 to 60 cm.) as the patient's condition seemed to be getting worse. Even these pressures did not prevent the cyanosis from advancing.

In summary, this was a case of acute poliomyelitis, in which the patient was greatly asphyxiated when placed in the respirator. Unfortunately, the paralysis was superimposed on a severe purulent bronchitis. Like L. C., the patient was given artificial respiration while flat on his back and in the horizontal position, when, after a few hours of relief, cyanosis appeared and began to deepen, the suction or inspiratory phase of the machine was increased.

Autopsy—The pleural cavities contained no fluid, and the surfaces were everywhere smooth in the right side of the chest. The left pleural cavity, however, showed old fibrous adhesions between the lower lobe and the parietal pleura in two places, one at the apex of the lower lobe. There were no recent adhesions. As soon as the chest plate was removed, a striking emphysema of the lungs and anterior mediastinum, due to small blebs, was noted. The emphysema in both lobes was limited to the crepitant portions, which were anterior and medial. There was striking emphysema of both the anterior and the posterior mediastinal spaces, that had undoubtedly developed from the associated emphysema of the lungs. The mediastinal tissues were puffed up with many small air-filled blebs, which were nearly confluent and covered the anterior surface of the pericardium. The right lung weighed 460 Gm and the left 440 Gm. Both showed the same picture.

Almost the entire lower lobe on each side was discolored a reddish purple, and was firm and heavy, owing to consolidation. Only the extreme anterior edge was somewhat pinker, and was crepitant, though not fully so. The middle and upper lobes showed the same discoloration, but to a distinctly less degree, and toward the apexes they were pinkish red but not purple. The posterior portions

Distribution of Lesions in the Lungs of Fifty-Six Cats Given Artificial Respiration in Horizontal and Head-Down Positions

Negative Pressure, Cm Water	Horizontal			Head Down		
	Number of Animals	Atelectasis and Hemorrhage	Atelectasis Only	Number of Animals	Atelectasis and Hemorrhage	Atelectasis Only
5	2	1	0	2	0	1
10	9	2	1	11	1	3
15	12	10	2	10	4	4
20	1	0	1	2	0	1
25	1	0	0	1	0	0
30	1	1	0	1	0	1
40	1	0	1	0	0	0
50	1	1	0	0	0	0
60	0	0	0	1	1	0
	28	15	5	28	6	10

of these lobes felt firm and slightly lumpy, strongly suggesting the feel of sago or tapioca pudding. The consolidated mass merged into the more crepitant mass rather indistinguishably. The lobes of each lung were incised posteriorly, and a considerable amount of thick bloody fluid flowed out freely. This was more prominent in the lower lobes, but was also present definitely in the upper lobes. Running the finger over the cut surface disclosed a consistency suggestive of tapioca. This consolidation gave a somewhat granular appearance, and when pressure was exerted mucopurulent material was expressed from the small bronchi and some pus from the alveolar spaces, in addition to the blood. There was an extensive bronchopneumonia, plus a mucoid or mucopurulent bronchitis, which had greatly hindered good aeration. When the bronchi were examined the mucosa was pinkish red, and there was a large quantity of tenacious mucopurulent material in practically all of the branches. This seemed to be about the proper consistency to interfere greatly with the passage of air in and out. The mucus bubbled easily. The emphysema in the lungs was limited to the pinker areas along the anterior margins and upper portions that were not dependent, and none was present in the grossly consolidated areas. Frequently the blebs were arranged in linear streaks on the surface of the lung toward the anterior free edge. Extending from the free edge toward the hilus there were definite streaks of emphysema, and these could be seen to follow the course of the blood vessels. It was surely

by this method that air escaped from the ruptured alveoli and followed the course of the blood vessels to the hilus and mediastinal tissues, where emphysema was also marked

Microscopic Examination—Numerous sections of the lung showed bronchitis, bronchopneumonia and emphysema. The degree of the pneumonic involvement and the age varied from an old process, in which the lung was completely solidified by an exudate composed of polymorphonuclear leukocytes and fibrin, to initial stages in which there was merely edema and congestion. In sections showing less extensive involvement the bronchi were filled with purulent exudate. Their epithelium was intact, and there was little infiltration of the adjacent tissues or alveoli. In others, there had been an infiltration of both the peribronchial tissue and the alveoli. Here and there the alveoli displayed a central oval or round, clear area surrounded by exudate, a condition due to entrapped air and often associated with an aspirational pneumonic process. A number of thrombosed blood vessels were seen, especially in one section that showed extensive involvement and in which the alveolar walls were identified with great difficulty, owing to necrosis and infiltration of polymorphonuclear leukocytes. The pneumonic process was essentially a bronchitis and peribronchitis which in places had progressed to a confluent bronchopneumonia. The more nearly normal lung tissue showed an acute emphysema with dilatation and rupture of the alveoli. There was a spreading of the tissue about the blood vessels, so that they appeared suspended in clear areas by a few strands of connective tissue.

In case 2 it was also necessary to begin artificial respiration after asphyxia had become dangerously advanced, in addition to this unfavorable circumstance, the patient was known to have a severe exudative bronchitis. It was impossible to change the patient's position. In our opinion, the exudate already in his lungs gravitated to dependent areas and gradually shut them off to aeration. This induced cyanosis, which was countered by increasing inspiration through increase of suction by the pump. This tended to spread and intensify consolidation, and eventually the suction was so far increased as to cause alveolar rupture and emphysema in the nondependent parts of the lungs capable of receiving air. In such cases one is confronted with the possibility of initiating a vicious cycle certain to be fatal if continued. One must realize that the breathing patient with a spreading bronchopneumonia, though dyspneic, probably never applies to his lung tissue the uniform pressure for air entrance of which the respirator is capable. If one lung shows most of the involvement, it is frequently more or less quiescent and cannot be forced out of this state even by inhaling excess carbon dioxide. Furthermore, when in such a patient the lung is so far filled as to leave but little space available for aeration, the patient does not overinflate this tissue. His power to breathe, like the rest of his muscular ability, succumbs slowly to lack of oxygen, and he dies. When, however, the respirator is used in connection with acute exudative

processes in the lungs, nothing protects affected areas against inflation. One must use the respirator under as low pressure as possible and must do all one can to prevent hypostatic spread of the condition by changing the position of the patient and by using the respirator at least for brief periods with the patient's head lower than his feet.

CASE 3—*A Premature Infant with Cyanosis*

L, a girl, aged 1 day, who weighed 1 pound, 11 ounces (765.44 Gm), was admitted to the Children's Hospital on Oct 17, 1929, because of poor condition owing to prematurity, as she was a seven months' child. Breathing was rapid and irregular, and the cry was weak. Cyanosis was present. The infant was placed in the respirator twenty-four hours after admission, and lived in it throughout the entire duration of the stay in the hospital, thirty-three days. For the first ten days the respirator was run for from ten to fifteen minutes every hour, or when a cyanotic attack occurred. A breathing rate of 40 per minute was employed, and a negative pressure of from 18 to 22 cm of water. After the first ten day period, and for the remainder of the child's life, the respirator was run almost continuously. Five per cent carbon dioxide and 95 per cent oxygen were frequently employed during the latter period. Throughout the period of treatment the infant was changed in posture, from back to side, always, however, with the body horizontal. The color was usually improved by the machine, but improvement did not always take place immediately. There was much mucus in the mouth at all times. During the fourth week of treatment, the temperature became unsteady and the cyanotic attacks more frequent. Death occurred on Nov 18, 1929.

This patient was a premature infant, very small indeed and subject to recurring attacks of asphyxia, who was treated successfully in the respirator for almost a month, when cyanotic attacks became very frequent, and death occurred in the fifth week. Though the position was changed very often, the head was never lower than the feet.

Autopsy Report—No fluid or adhesions were observed in the pleural cavities. The surfaces were all smooth and glistening. The right lung weighed 15 Gm, the left lung, 12 Gm. Both were distended and normal in shape, except for their borders, which were somewhat collapsed and atelectatic. The visceral pleura was thin and transparent, but had a slight grayish tint. The underlying interlobular septums were quite distinct, and the outlined lobules of the substance of the lung on close inspection appeared slightly raised as if they were overdistended. Except for the atelectatic borders, these emphysematous-like areas were scattered diffusely over the surfaces of the lungs. Externally, the lungs were pinkish red, with small, dark bluish-red patches suggesting small terminal hemorrhages. Both lungs floated, but were less crepitant and slightly firmer than normal. On section the cut surfaces were reddish, except for the small dark hemorrhagic areas, and yielded only reddish fluid on pressure. No pus or areas of consolidation were seen. No thrombi were found in the pulmonary vessels. The bronchi were traced, and the mucosa was found to be smooth and pale throughout.

Microscopic Examination—Three sections showed a number of alveoli packed with red blood cells and an occasional leukocyte. No purulent exudate was seen in the alveoli or bronchi, except for a single alveolus, which contained many leukocytes and desquamated epithelial cells. Two sections showed marked atelectasis. A few alveoli were partially distended. The intervening lung tissue was represented by thick masses of epithelium and had an immature appearance. The cells were large, round or oval, and densely packed. The capillaries in these

atelectatic areas were congested. The bronchi were contracted, and occasionally contained red cells and desquamated epithelial cells.

In nonatelectatic areas the alveoli were normally dilated. In the main, the walls were thicker than normal, but in some regions there was definite thinning and emphysema. The bronchi appeared dilated, and not infrequently contained masses of red cells.

In this case and that of five other premature infants showing similar lesions at autopsy, the characteristic damage of the lungs consisted of small hemorrhagic patches scattered through the lungs and tending, in several cases, to be more numerous posteriorly and toward the bases of the lungs. Coupled with this simple hemorrhagic lesion were varying amounts of emphysema and of lung tissue that had never expanded. In no case was there bronchopneumonia, though it seemed certain that it would have occurred had time for development been given. In every instance the hemorrhagic condition was recent and but shortly antedated death. This was evidenced by the entire freshness of the extravasated blood, the lack of reaction about the hemorrhagic areas and the small amount of blood that had moved into the bronchioles. We believe that the hemorrhagic lesions represent alveolar ruptures due to overdistention by the respirator while the alveolar circulation was good. If such rupture did not occur, the area in question gradually reached the relatively bloodless condition characteristic of emphysema, and then if rupture did take place no hemorrhage occurred, and one noted the dry emphysema found characteristically through all the lungs examined. The persistence of numerous atelectatic areas in the lungs of a child who was treated in the respirator for five weeks makes it seem probable that one cannot open the lungs with any reasonable use of the respirator.

Finally, the question arises as to what measures might have been taken to avoid the lesions of the lungs, scattered hemorrhages and emphysema that were found regularly at autopsy. Frequent changes in position are unquestionably of importance. They have a marked effect in preventing the gravitational filling of bronchioles by fluid from the upper air passages. It requires but few experiments on cannalized animals to convince one of the ease with which even viscous fluids placed in the lower part of the trachea are distributed by gravity through the lungs. If the respirator is operating with a degree of inspiration producing suction about as great as the lung tissue can tolerate, the sudden plugging of a bronchiole with the prevention of ingress of air apparently subjects the alveoli served by this bronchiole to a degree of trauma apt to bring about rupture. It was our opinion that much of the hemorrhagic exudate seen in the second adult case, that

of H P, was produced in this way. The presence of excess mucus in the mouth and upper air passages of premature infants is often troublesome, and was markedly so in the case that we have reported. Yet the bronchioles were not significantly filled with material of any kind. It is thus reasonable to believe that no more than a small share of the observed damage was created by the bursting of alveoli served by a plugged bronchiole. The experiments on animals reported later in the paper indicated that periods of respiration with the head lowered offer the best means for avoiding such damage. But in these infants, on whom careful observation during life can be coupled with observations at autopsy, it seems possible that most of the trauma that produced hemorrhage was an expression of brief periods of unresisted overventilation applied to relieve cyanosis that may have been due to a variety of causes. This again means that in infants, as in adults, the respirator should not be run with more than the minimal amount of suction capable of sustaining life. In contrast to the cases of patients with complete respiratory paralysis, the premature infants breathed, though at times inadequately. They did not fall in with the rhythm of the respirator as does a conscious adult. One should use the respirator when the breathing of the child becomes inadequate, and should interrupt the action so as to allow the child to breathe by itself as soon as it is able to do so.

Last of all, it should be pointed out that the observations on these six premature infants, five of whom weighed less than 3 pounds (1,360 Gm) and all of whom were regarded as hopeless risks on admission to the hospital, in no sense condemn the respirator for use in similar cases and for use on asphyxiated full term infants. Von Wachenfeldt,⁴ using a similar type of respirator, evolved independently as a result of unsuccessful experiences with the baby barospirometer of Thunberg⁵ in the treatment for asphyxia neonatorum, reported excellent results in full term infants. It has been our desire to show that in desperate cases certain similar lesions are found and to indicate as well as possible the cause of these lesions and the best means of combating their occurrence.

EXPERIMENTS

Animal experiments bearing on our clinical observations have been easy to construct. We have desired to know three things: (1) whether over-respiration of curarized animals would produce the hemorrhagic lesions that we have found in patients, (2) the degree to which material in the bronchi increases their occurrence, and (3) the best means of avoiding such damage.

Cats were employed. In every case the procedure was as follows. The animal was anesthetized with ether. A cannula was tied in the femoral vein through

4 von Wachenfeldt, S. *Acta obst et gynec Scandinau* 9:600, 1930.

5 Thunberg, T. *Scandinau Arch f Physiol* 48:80, 1926.

which the injections of curare were made. Another cannula was inserted into the upper part of the trachea. The animal was placed in the respirator with his head protruding through the rubber collar at one end. At this time 15 cc of 1 per cent curare was injected into the femoral vein, which was followed by complete respiratory paralysis within thirty seconds. The respirator was closed, and artificial respiration was begun.

In order to kill the animal it was bled from the carotid artery. Immediate autopsy was performed on the lungs. The trachea was tied tightly with a heavy cord, after which the anterior wall of the chest was removed, and its contents were taken out en masse. Pictorial records were made of any superficial lesions, and the bronchi were explored in cases in which gross lesions were observed.

Twenty-eight animals were given artificial respiration under varying amounts of negative pressure, while in the horizontal position. A second group, under the same negative pressures but with the head down, were compared with these. A 10 to 20 degree inclination was used. When the damage of the lungs was found, it appeared grossly as rather sharply margined solid dark red areas which, on microscopic section, proved to be atelectatic and usually showed alveoli containing blood. Emphysema occurred, but was always slight. The accompanying table shows the distribution of the lesions. It is unfair to the head-down position, in that it gives absolute frequency and no indication of the degree of damage that was found. This was decidedly less in the head-down position, though numerically as given in the table. The distribution of the lesions was irregular, but in general they were most frequent in the dependent parts of the lungs. For the animals in the horizontal position this meant the posterior parts of the lower lobes, and for the inclined animals the posterior parts of the upper lobes. The length of the experiments was usually one hour, though several of the animals in the head-down position under 10 cm of negative pressure were carried for twelve hours and maintained in excellent condition. In many instances it was possible to show that the characteristic lesion was associated with a plugged bronchus or bronchiole, and, though not invariably demonstrated, we feel that this was invariably the case. Etherization of cats invariably induces a great deal of saliva and mucus. This material, if it becomes intratracheal, will find its way into dependent bronchioles, this occurs particularly under conditions of respiratory paralysis. The head-down position helps materially to prevent this gravitational movement. One can see this clearly if a cat is prepared according to the method used in these experiments and if heparinized cat plasma heavily colored with methylene blue is introduced through a tracheal catheter. If the animal is horizontal this artificial exudate, even under the gentlest artificial respiration, flows into the dependent parts of the lungs, and within a short time causes the appearance of large areas of atelectasis and hemorrhage. When the animal is placed at a 20 degree angle, the injected fluid slowly flows out of the mouth, and one rarely sees lesions of any sort.

A final observation, particularly on the animals in which respiration was produced under high negative pressures, was a definite and generalized pulmonary congestion. If the respirator is used with too great negative pressures one may apparently count on increasing the amount of blood in the lungs and thus favor the induction of both edema and hemorrhage.

COMMENT

On the basis of our clinical experience and experiments, we shall now turn to the questions that were asked in the early part of the paper.

and that are of vital importance to any one using the respirator. First, can one give any definite direction as to the degree of negative pressure that can be applied with safety? In completely paralyzed adults one may apparently expect to do harm if the negative pressure is greater than 25 cm of water for any considerable time. This will consist in the appearance of scattered hemorrhagic areas, and these are almost invariably associated with bronchial plugging. The danger of producing them will be greatly reduced by frequent changes in the position of the patient and by the head-down position. This position should always be used when there is evidence or suspicion of excess fluid in the air passages. Second, if cyanosis deepens under moderate use of the respirator, that is, with negative pressures under 20 cm of water in adults, should one increase the negative pressure to provide relief? At the most, such an increase should be for a very brief period—not more than a minute—since it is certain that if the cyanosis is due to filling the lung with exudate the increased negative pressure will do harm rather than good. If the cyanosis is cardiac in origin, nothing will be gained by the movement of more air. Third, are there special precautions to be taken in using the respirator on infants? Our experience is still rather limited, but it would seem that prolonged use of negative pressures above 10 cm of water are dangerous. Owing to the fact that infants are almost certain to have excess mucus and fluid in the bronchi, it is imperative that they be inclined at an angle of from 10 to 20 degrees and the position changed frequently. A rate of about 35 per minute is apparently satisfactory.

SUMMARY

1 Clinical and postmortem data for two adults and six infants treated for respiratory failure in the Drinker respirator are given.

2 These data show that for long periods the respirator should be used with as low negative pressures as possible, not more than 25 cm of water for the adult and 10 cm of water for the infant.

3 Patients with the combination of an exudative process in the lungs and respiratory paralysis make little progress when placed in the respirator. At autopsy they show hemorrhagic lesions which, in our opinion, may have arisen following bronchiolar plugging and atelectasis. Such patients should always be treated in the head-down position and changed from back to side if it is possible to do so.

4 Infants should not be subjected to negative pressures greater than 10 cm of water for long periods, and they should invariably be treated with the head down at an angle of from 10 to 15 degrees.

5 Experiments on animals that bear on these points are discussed.

ANEMIA ASSOCIATED WITH CHRONIC DYSENTERY

CLINICAL CONSIDERATIONS, WITH SPECIAL REFERENCE TO THE
CAUSE AND TREATMENT *

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In a previous paper ¹ we emphasized the importance of nutritional disturbances in the production of anemia in patients with chronic dysentery. In studying further a number of these patients, we were impressed by the similarity between many of the clinical features observed and those which are said to be characteristic of pernicious anemia. In this paper we present our clinical observations and discuss the cause and treatment of the anemia encountered in a group of sixteen patients.

METHODS OF STUDY

All of the patients were studied while resident in the Peiping Union Medical College Hospital. The diagnosis of chronic dysentery was made on a basis of the clinical history, including the course of the disease, the observation of characteristic ulcers in the colon on sigmoidoscopic examination and from cultivating dysentery bacilli from the stools. The red blood cells were counted in the usual way, and the hemoglobin content of the blood was determined in a Sahli hemoglobinometer that had been standardized with the oxygen capacity method so that 100 per cent was equal to 17 Gm. of hemoglobin per one hundred cubic centimeters of blood. The reticulocytes were counted, the dry smear technic being used. Gastric analyses were done following the injection of 0.5 mg. of histamine, and the highest acid value obtained during the test was noted. In case no free acid appeared following the injection of histamine, the test was repeated at various intervals during the course of the illness to determine whether or not the ability of the stomach to secrete acid changed. The diameters of the erythrocytes were obtained by direct measurement of 500 cells, an ocular micrometer that

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1. Keefer, C. S., Huang, K. K. and Yang, C. S. The Importance of Undernutrition in the Production of Anemia Associated with Chronic Dysentery and Tuberculosis of the Intestine, *Nat. M. J., China* **15** 743, 1929.

had been properly calibrated being used. The Price-Jones curves were plotted from these data. The treatment of the patients varied according to individual circumstances. In the early part of our investigations, when we were more conservative, we used transfusion of blood as a therapeutic measure. In some cases other forms of therapy were instituted immediately, because the patients were very ill, while in others, a control period was observed before special therapy was begun. When liver extract was given, the product manufactured by the Parke, Davis Company was used in amounts equivalent to 300 or 500 Gm of whole liver a day. When whole liver was given, it was mixed with rice or soup. Iron was administered in the form of pills of ferrous carbonate U S P, in amounts varying from 0.9 to 4.8 Gm daily.

INCIDENCE OF ANEMIA IN PATIENTS WITH DYSENTERY

While anemia has been recognized as a complication of dysentery and reported by Seyderhelm,² Lepehne,³ Oestrich,⁴ ourselves¹ and others, most of the reports have been of small groups of cases. To gather information regarding the presence of anemia in patients with dysentery observed in our medical clinic, we studied the clinical records in 350 proved cases. The results are tabulated in figure 1. The cases were divided into two groups: those with chronic dysentery (group A) and those with acute dysentery (group B). Those in group A had had symptoms of dysentery for two months or longer while those in group B had had symptoms for less than two months. While we appreciate the difficulty of attempting to classify one case as acute and the other as chronic and separating them on a basis of the duration of the illness being under or over two months, we selected this period of time as the dividing line because fifteen of the sixteen patients studied had anemia associated with active dysentery for over two months. We believed, therefore, that if other cases were to be compared, it would be desirable to divide the cases in this way. Figure 1 shows that anemia was more common in group A than in group B. The various factors that explain this difference will be discussed.

REPORT OF ILLUSTRATIVE CASES

CASE 1—*A man with chronic dysentery, anemia, atrophy of the papillae of the tongue, normal gastric acidity and no signs of degeneration in the central nervous system improved remarkably following liver extract. The anemia improved, and the tongue became normal in appearance.*

² Seyderhelm, R. Die Pathogenese der perniziösen Anämie, *Ergebn d inn Med u Kinderh* **21**:361, 1922.

³ Lepehne, G. Zur Frage der intestinalen Genese der perniziösen Anämie, *Med Klin* **21**: 205, 1925.

⁴ Oestreich, Carl. Ueber die Häufung der Fälle von Anämia perniziösa, ihre Ursache und einige prinzipielle Gesichtspunkte, *Krankheitsforschung* **2**: 389, 1926.

History—A soldier, aged 23, was admitted to the hospital on account of diarrhea of two and one half months' duration. For several months previously he had suffered from excessive exposure to cold and was unable to obtain adequate amounts of food. His diet had consisted of bread, vegetables and noodles. He was unable to obtain meat. Otherwise his personal history was unessential.

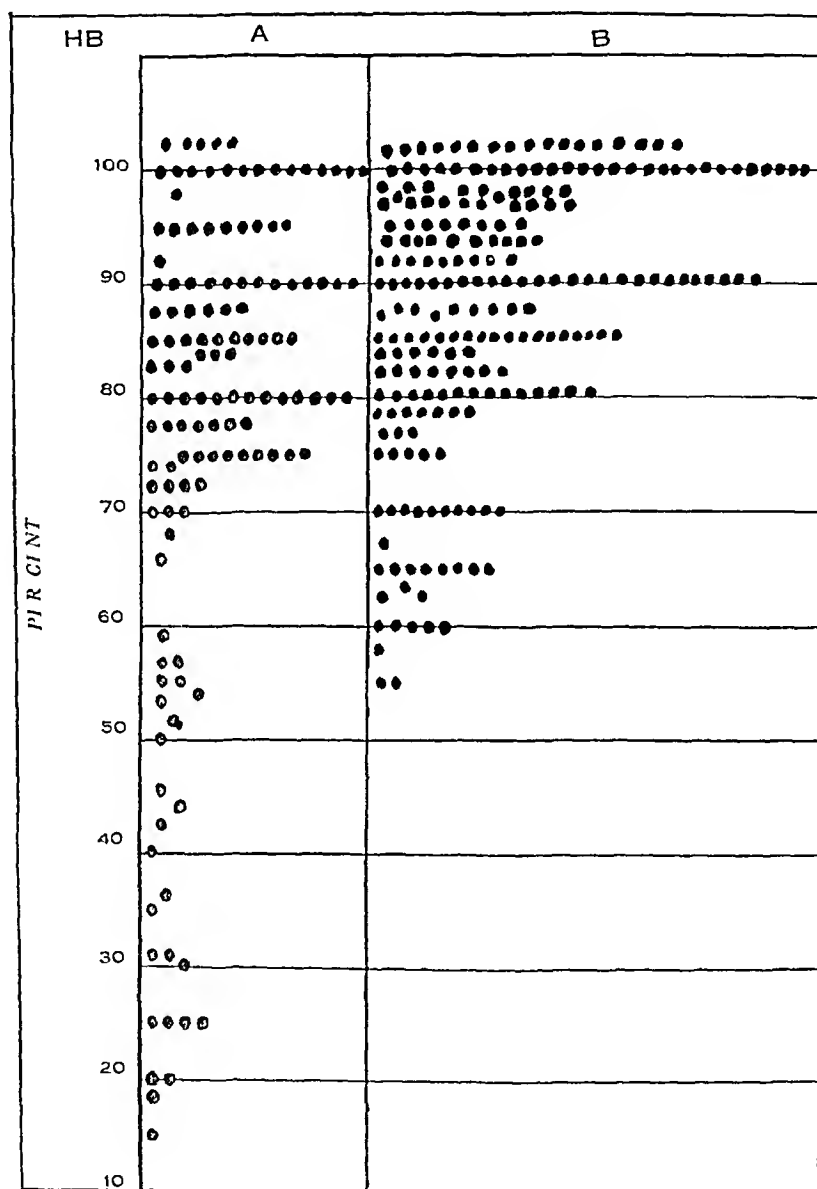


Fig 1—Group *A* represents the hemoglobin content of the blood of patients with dysentery of more than two months' duration, group *B*, the hemoglobin content of patients with dysentery of less than two months' duration. Each dot represents the hemoglobin content of one patient.

Ten weeks before coming under observation he began to have severe generalized abdominal pain and diarrhea associated with tenesmus. The stools were of thin consistency and contained moderate amounts of mucus streaked with blood. The bleeding was never excessive and was present for only the first two weeks of his illness. He had lost weight and strength, and for several weeks had noticed increasing pallor and breathlessness on exertion.

Examination—On examination, the patient was found to be afebrile and mentally clear, but emaciated and pale. There was neither edema nor jaundice. The skin was normal. The eyes were normal in appearance, and the pupils active. The ocular fundi showed marked pallor with numerous retinal hemorrhages about the disks and in the region of the macula. There were irregular patches of exudate in the lower temporal field of the left eye and the upper nasal field of the right eye. The mucous membranes were pale, and the nose and throat were normal in appearance. The tongue presented an interesting picture, as the normal gray coating was absent. The median surface of the anterior two thirds was quite smooth, and the papillae had completely disappeared. At the margins a few small filiform papillae could be seen. The tongue had never been sore or painful, and no symptoms suggesting stomatitis or glossitis had been manifested.

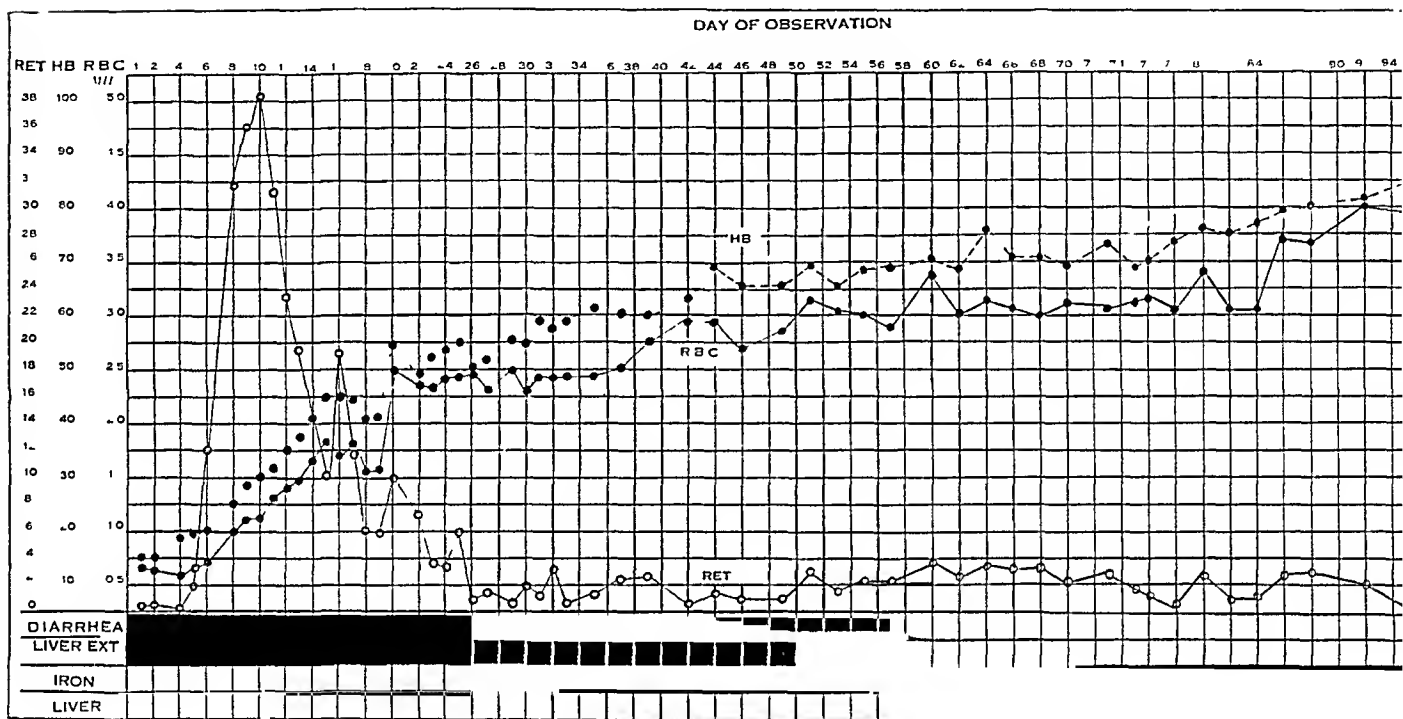


Fig 2 (case 1)—Chart of a patient with chronic dysentery and anemia, showing marked improvement following liver extract therapy. The reticulocytes, hemoglobin and erythrocytes increased in spite of the presence of severe diarrhea. Following the maximum improvement after treatment with liver extract, the patient recovered gradually on iron, and whole liver and iron therapy.

The organs of the neck were normal. The heart and lungs were clear. The abdomen was moderately distended, and on palpation tenderness was present over the ascending and descending colon. The liver, spleen and kidneys were not palpable. The extremities were normal. There were no demonstrable changes in the central nervous system. The reflexes, muscular power and sensations were normal. The lower colon was examined with the sigmoidoscope, and found to be pale and covered in numerous places with a diphtheritic exudate. When this membrane was removed, numerous, shallow, irregular ulcers were seen. The scrapings from the ulcers did not reveal *Amoeba histolytica*, but bacteriologic cultures showed both mannite-fermenting and the Shiga type of dysentery bacilli.

Examination of the blood showed red blood cells, 600,000 per cubic millimeter, hemoglobin, 16 per cent, leukocytes, 4,350 per cubic millimeter, with 48

per cent polymorphonuclears, 45 per cent lymphocytes and 7 per cent monocytes. The bleeding and clotting times were normal. The icterus index was normal. The platelets were reduced to 140,000 per cubic millimeter. The hematocrit reading revealed only 7 per cent cells, and the volume index was 115. The stained smear showed a marked variation in the size and shape of the erythrocytes. The reticulocytes were 18 per cent, and 3 nucleated red blood cells were seen in counting 300 nucleated cells. When the diameter of 500 erythrocytes was determined by the direct micrometer method, it was found that the average diameter was 6.04 microns. The Price-Jones curve showed a shift to the left. The Wassermann and Kahn reactions of the blood were negative. The total

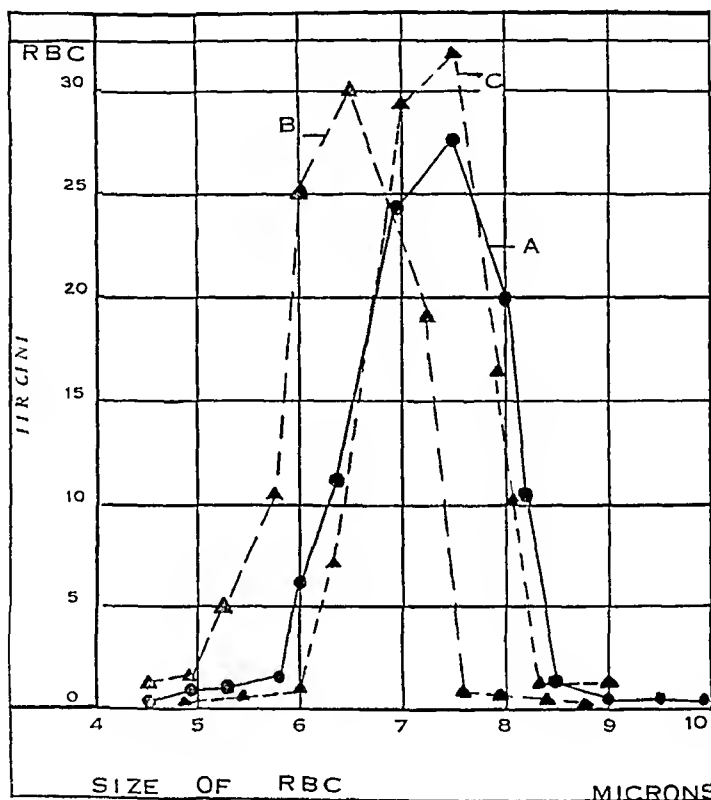


Fig. 3 (case 1)—Price-Jones curves of the blood. Curve B represents the size of the red blood cells before treatment and curve C after recovery from the anemia. Curve A is an average normal curve.

serum protein was 4.5 per cent. The indirect van den Bergh reaction was 1.3 units. The nonprotein nitrogen was 19 mg per hundred cubic centimeters of blood.

The stools were liquid and varied from ten to thirteen a day. They contained mucus, red blood cells and leukocytes. On bacteriologic examination, *B. dysenteriae* of the manure-fermenting and Shiga variety were found. The urine was normal. A teleoroentgenogram of the heart showed it to be of normal size, and the electrocardiogram showed a normal mechanism. The gastric analysis showed 24 per cent free hydrochloric acid, with a total acidity of 42 per cent after injection of histamine. The course of the red blood cells, hemoglobin and reticulocytes can be followed in figure 2. The Price-Jones curves made at different intervals during the period of observation are shown in figure 3. A photomicro-

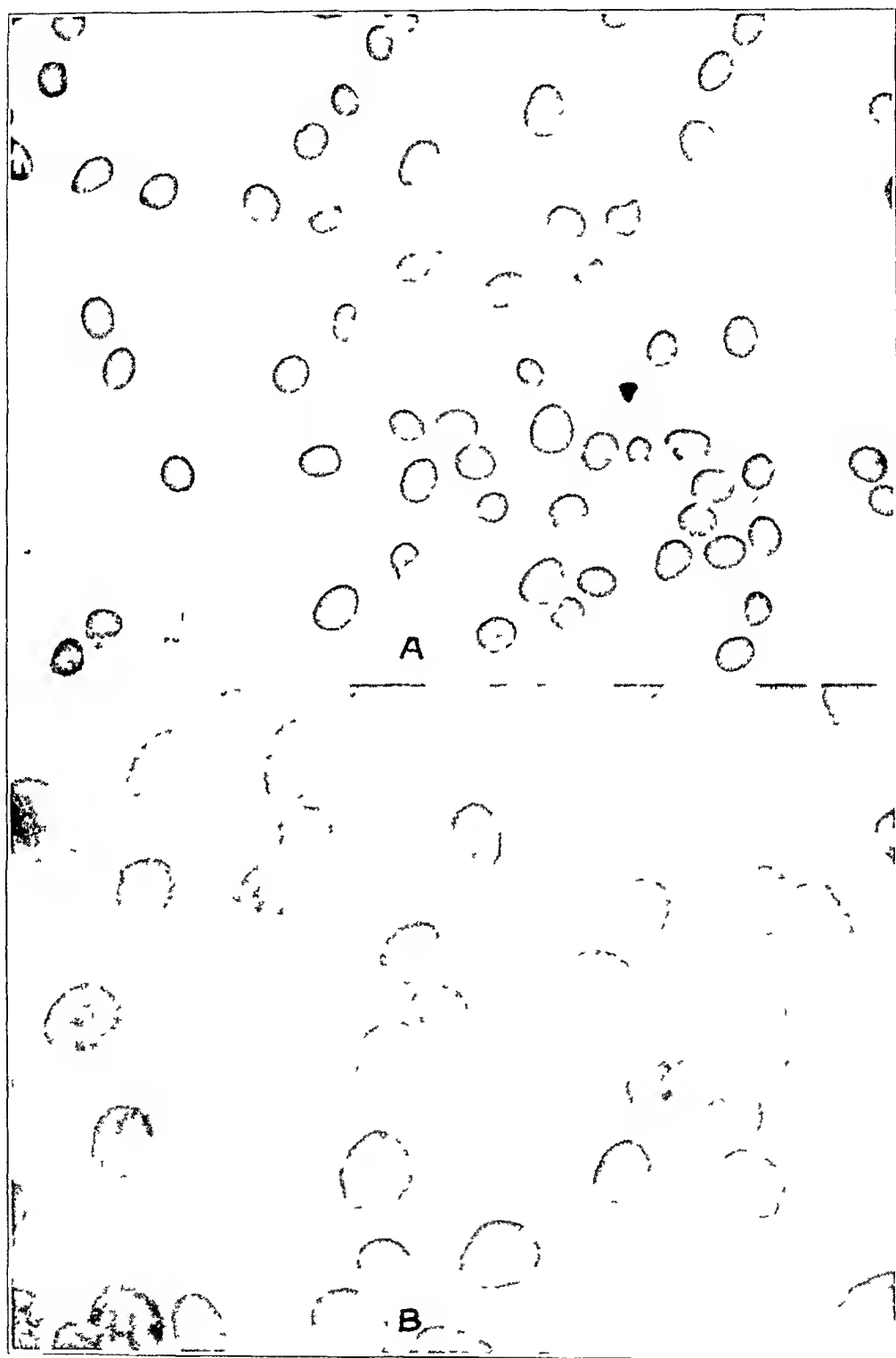


Fig 4 (case 1)—Photomicrographs of the blood, *A*, before treatment with liver extract, $\times 600$, *B*, after treatment with liver extract, showing an increase in the reticulocytes, $\times 1,000$

graph of the blood on admission may be found in figure 4A, and figure 4B shows the shower of reticulocytes following treatment with liver extract

Course of Illness Following Treatment—The patient was kept at rest in bed. He was placed on a diet of milk and liver extract given in amounts equivalent to 500 Gm of whole liver daily. In spite of the persistence of the diarrhea, the hemoglobin and red blood cells increased rapidly, and the reticulocytes were increased to 38.4 per cent within ten days of the beginning of treatment. During this time the papillae of the tongue returned, and the normal gray of the surface reappeared. The change in the appearance of the tongue is illustrated in figure 5. During this time the patient lost 10 pounds (4.5 Kg) in weight. After twenty days, the blood count became stationary and the reticulocytes were normal by the twenty-sixth day. Iron was then substituted for the liver extract. It was given in the form of 4.8 Gm of ferrous carbonate pills daily. After twenty-two days on this treatment there was slight improvement, and liver extract was again added to the diet. Later whole liver was substituted for the liver extract. The diarrhea gradually disappeared, the blood count and hemoglobin returned to normal, the weight of the patient increased 20 Kg, and he appeared normal.



Fig 5 (case 1)—Tongue of the patient with anemia associated with chronic dysentery. Note the atrophy of the papillae of the median surface of the tongue in A. The condition of the tongue following recovery from anemia is shown in B.

Comment—A young man who had been on an inadequate diet suffered from chronic bacillary dysentery. Physical examination revealed hemorrhages in the eyegrounds, atrophy of the papillae of the tongue, severe anemia, leukopenia and reduction in the number of platelets. The red blood cells were smaller than normal, and there were only a few reticulocytes and an occasional nucleated erythrocyte. There was no alteration in gastric secretory function, and examination of the central nervous system revealed nothing abnormal. On treatment with liver extract, the anemia improved, the reticulocytes increased, the tongue became normal in appearance, the average diameter of the red cells increased, the platelets increased, the white blood cells became normal, and the retinal hemorrhages disappeared. The patient continued to improve gradually, gained 10 Kg in weight and was discharged as well.

CASE 2—A young man, aged 22, with chronic bacillary dysentery, hyperchromic anemia, edema disease normal gastric acidity, normal tongue and central nervous system, recovered spontaneously on a hospital diet

History—A shoemaker was admitted to the hospital complaining of diarrhea. He had always enjoyed good health. Four months before entrance he began to have diarrhea, and the stools contained some mucus streaked with blood. The acute symptoms persisted about two weeks, and then the illness was characterized by a persistent diarrhea without blood or mucus in the stools. As a result of this malady, the patient lost weight and strength, and twenty days before admission he began to notice swelling of the lower extremities and face. His diet had consisted of vegetables, wheat cakes and steamed bread. He had not eaten meat for approximately six months. The only feature of interest in his previous history was an attack of dysentery eighteen months previously.

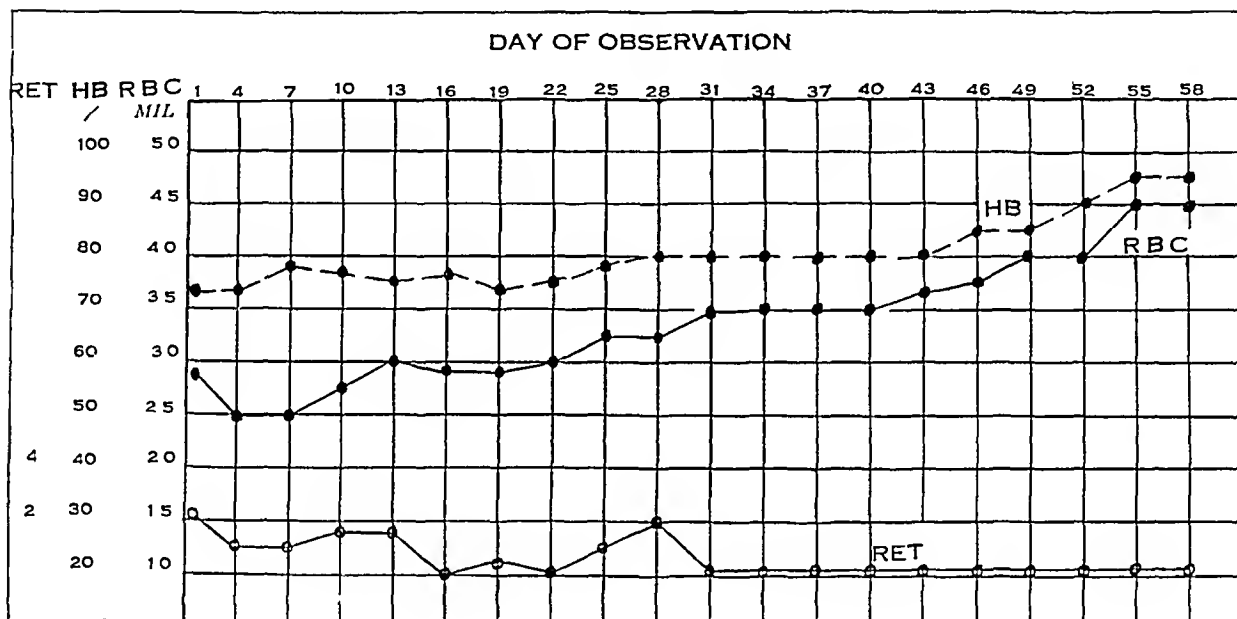


Fig 6 (case 2)—Chart of a patient with hyperchromic anemia associated with chronic dysentery and edema, showing the course of recovery on hospital diet

Examination—On examination, it was found that he had a generalized anasarca. The face, the wall of the chest, the back and legs were swollen and showed pitting on pressure. There was no demonstrable fluid in the serous cavities. The mucous membranes were pale, the eyes normal and the pupils active. The tongue was normal in appearance. The organs of the neck, the heart and the lungs were normal. The liver and spleen were not enlarged. Examination of the reflexes and the different modalities of sensation revealed nothing abnormal. Sigmoidoscopic examination of the colon showed a number of ulcers from which *B. dysenteriae* were cultured. Gastric analysis following the administration of histamine showed a free acidity of 38 per cent and a total acidity of 59 per cent.

Examination of the blood revealed erythrocytes, 2,750,000 per cubic millimeter, hemoglobin, 72 per cent, color index, 1.25, reticulocytes, 4 per cent, white blood cells, 12,250. The Price-Jones curve showed a spreading of the base of the curve and a shift to the right of the normal curve (curve B, fig 6). The Wassermann reaction of the blood was negative. The urine was clear and did not show albumin.

Course of Illness—Following the ordinary hospital diet, which consists of approximately 72 Gm of protein, 42 Gm of fat and 345 Gm of carbohydrate, the patient recovered slowly. The edema disappeared, and the erythrocyte count and the hemoglobin content of the blood returned to normal in fifty-eight days. The changes in the blood can be followed in figure 6.

Comment—A man who had been on an inadequate diet developed dysentery, hyperchromic anemia and edema. Following an adequate diet the edema disappeared and he recovered from the anemia.

CASE 3—*A man with chronic dysentery, intestinal polyposis, stricture of the colon and diarrhea, developed marked undernutrition, pellagra and severe anemia. No improvement of the anemia resulted following the administration of liver extract. Remarkable recovery resulted after whole liver and iron were given.*

History—The patient was admitted to the hospital on account of diarrhea, weakness, numbness of the legs and the presence of an eruption over the backs of his hands. He was a cart driver and a vegetarian. His food consisted chiefly of millet and salted vegetables. The present illness began one year before admission with an attack of acute diarrhea and high fever. The stools contained mucus streaked with blood. The diarrhea persisted, and six months later he became bedridden. He lost weight and became progressively weaker. The legs were numb, and an eruption appeared over the dorsa of the hands.

Examination—On examination, the patient was found to be extremely weak, emaciated, pale and somewhat confused mentally. The skin was dry and scaly. The tongue showed a superficial glossitis, with accentuation of the fissures. Over the dorsal surfaces of both hands was an eruption characteristic of the lesions of pellagra. The lesions were almost mirror images, distributed symmetrically, with patches of hyperpigmentation. There were no lesions about the neck, feet or genitalia. The lungs were clear. The heart was not enlarged, and the sounds were normal. The abdomen was moderately distended. The spleen was palpable below the costal margin, but the liver could not be felt. There was some tenderness over the sigmoid colon in the left lower quadrant, but no definite masses were felt. There were signs of a mild peripheral neuritis over the legs. The Wassermann reaction was negative. The gastric analysis following the histamine test showed a low gastric acidity with a free acid of 6 per cent and a total acidity of 18 per cent. There was a severe anemia, its course can be followed in figure 7. The sigmoidoscopic examination showed some narrowing of the lumen of the rectum and sigmoid with many ulcers and polypi. In other words, a picture characteristic of a long-standing, ulcerative colitis was present.

Course of Illness—The patient was given the usual hospital diet supplemented with fresh cow's milk, yeast and tomato juice. There was no improvement in the anemia following this diet. Practically no improvement followed the addition of liver extract or whole liver. However, when iron was added to the whole liver, the improvement of the anemia was striking. The patient's general condition improved, he gained weight, the diarrhea diminished, the signs of peripheral neuritis gradually disappeared, and the skin resumed a normal appearance.

CASE 4—*A man with chronic dysentery developed anemia and recurrent attacks of glossitis, with papillary atrophy. Moderate improvement followed administration of liver extract and iron, with the disappearance of glossitis and the reappearance of the papillae of the tongue. The anemia improved gradually.*

History—A man, aged 38, was admitted to the hospital on account of recurring attacks of sore mouth and diarrhea. One year previously, he had begun to have an intermittent diarrhea, which persisted until admission. Several weeks before he entered the hospital, the diarrhea became much more severe, and blood and mucus appeared in the stools. Soon after the onset of the disease he began to have attacks of stomatitis and glossitis. These attacks were associated with a sensation of burning and pain on mastication. For several months he had noticed progressive weakness, but had never been confined to bed.

Examination—On examination, he appeared somewhat weak and pale. There was no jaundice. The tongue was large, red and smooth. The papillae had disappeared from the anterior two thirds of the tongue, leaving a smooth, shiny surface. The mucous membranes were red, but there were no ulcers. The heart and lungs were normal. The abdomen was slightly distended, and there was some

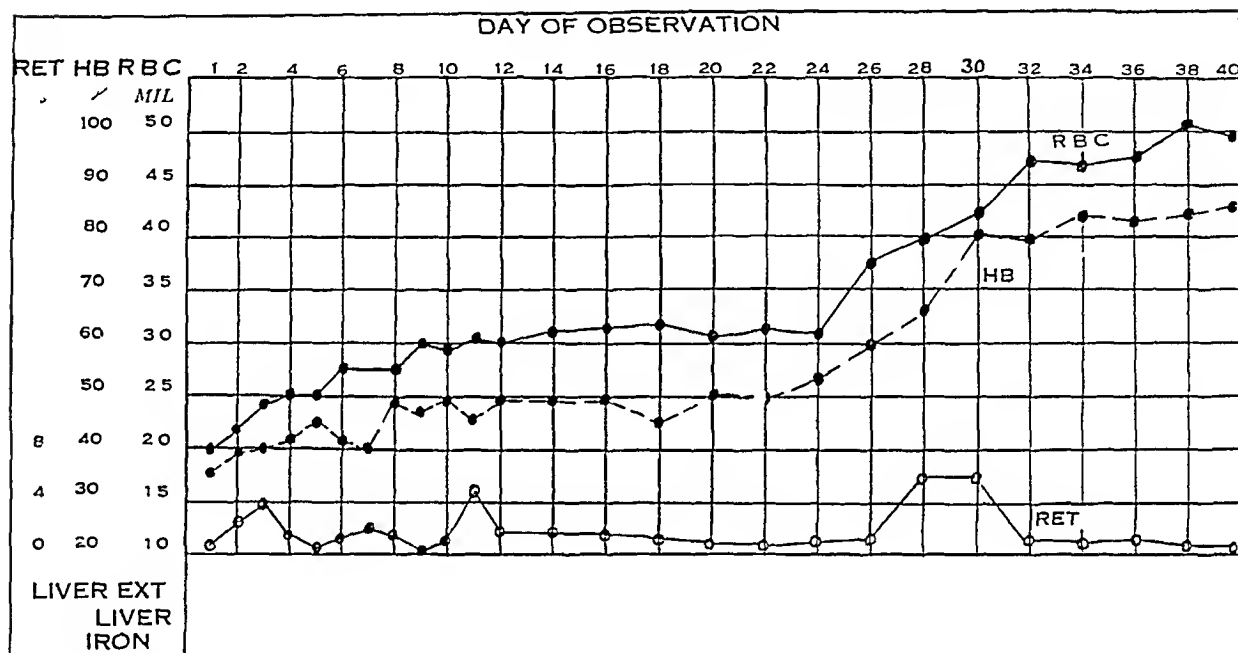


Fig 7 (case 3)—Chart of a patient with anemia associated with chronic dysentery, polyposis of the colon and pellagra, who showed no response to liver extract or whole liver therapy, but an excellent response following the administration of iron.

tenderness over the sigmoid colon. The patient had diarrhea, and the stools were characteristic of bacillary dysentery. Sigmoidoscopic examination revealed numerous small ulcers from which *B. dysenteriae* of the mannite-fermenting group were cultured. The Wassermann reaction was negative. Gastric analysis revealed a complete absence of free hydrochloric acid following the histamine test.

The course of the patient's blood can be followed in figure 8. Figure 14 illustrates the appearance of the tongue on admission and following treatment. It may be noted that the tongue assumed its normal appearance with the return of the papillae. The acid did not return in the gastric juice.

CASE 5—A man with chronic dysentery, anemia, atrophy of the papillae of the tongue, temporary gastric anacidity and signs of degeneration on the posterior columns of the spinal cord improved following administration of liver extract and iron. The tongue became normal, acid returned in the gastric juice, and there was moderate improvement of the subacute combined sclerosis.

History—A man, aged 46, was admitted on account of recurrent attacks of diarrhea of seven years' duration. The attacks usually occurred in the summer months and were associated with tenesmus, abdominal pain, nausea and vomiting. For two years, the diarrhea had been more or less continuous, and the frequency of the stools had increased shortly before entrance. For several months he had noticed progressive pallor, dizziness and tinnitus. His personal history was inconsequential.

Examination—On examination, the patient was found to be undernourished and pale. The skin was normal in appearance, and there was no jaundice. The eyegrounds were normal. The mucous membranes were pale. The tongue was smooth and shiny, and there was a complete atrophy of the papillae in the central portion of the anterior two thirds. The organs of the neck, the heart and the

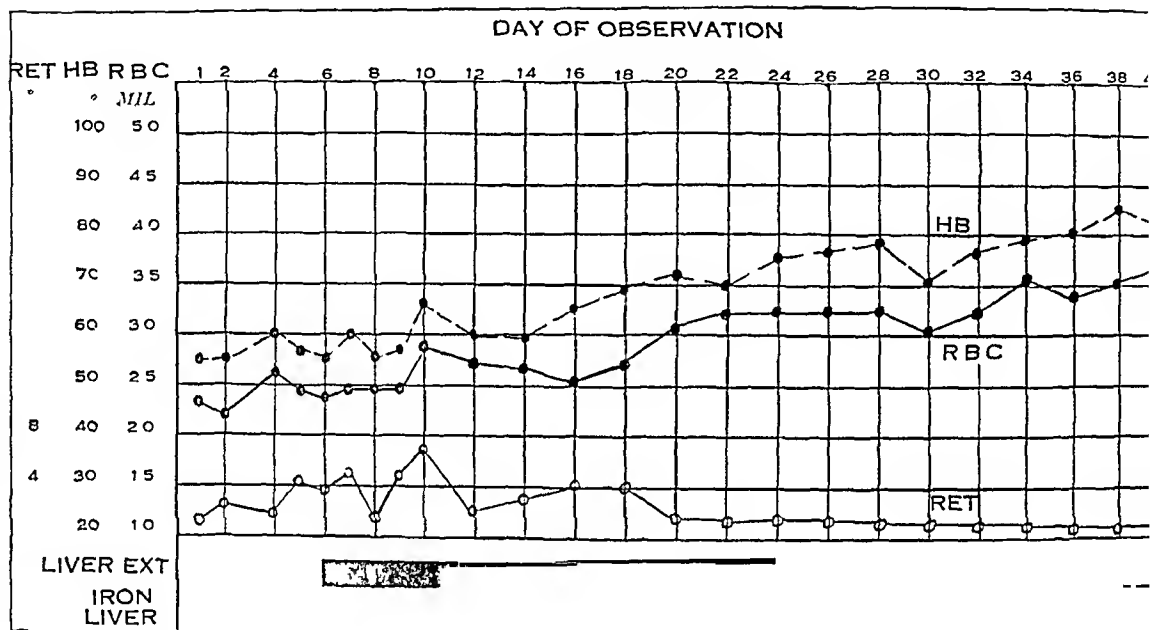


Fig 8 (case 4)—Chart of a patient with anemia, glossitis and gastric acidity, who showed gradual recovery from the anemia following the administration of liver extract and iron, and whole liver and iron.

lungs were normal. There was slight tenderness over the descending colon. The liver and spleen were not palpable. The extremities appeared normal. The knee and ankle jerks were absent, and there was definite ataxia when the knee-heel test was performed. There was a loss of vibratory sense below the knees, and a loss of sense of position of the toes. On sigmoidoscopic examination of the colon, numerous small ulcers were found, and *B. dysenteriae* were grown from the scrapings. Gastric analysis following the histamine test failed to reveal acid in the gastric contents. The urine was normal.

Examination of the blood revealed 3,000,000 erythrocytes, 50 per cent hemoglobin and 0.5 per cent reticulocytes. No nucleated cells were seen. The average diameter of the red cells was 7.3 microns. The Price-Jones curve showed practically a normal curve with a slight widening of the base and a shift to the right. The Wassermann test of the blood was negative. The stools were liquid in consistency and contained mucus and a few red blood cells.

Course of Illness—On rest in bed, hospital diet and treatment of the dysentery by means of irrigations of the colon using Dakin's solution, the patient's general condition and dysentery improved. The course of the blood can be followed in figure 9. There was improvement of the anemia without the addition of liver extract or iron to the therapy. Later, liver extract, alone and in combination with iron, was added, and the red count and hemoglobin returned to normal. As the patient improved, the tongue became normal in appearance, and the papillae returned. The stomach also regained the ability to secrete free acid following the injection of histamine. The sensory disturbances over the legs became less marked, but the knee and ankle jerks continued to be absent. On discharge from the hospital the patient appeared quite normal.

CASE 6—A boy who had lived on a poor diet developed dysentery, anemia and edema. Improvement in the anemia followed upon therapy.

History—A pedler, aged 18, was admitted to the hospital on account of diarrhea which had been present for two months. Before the onset of the illness, he

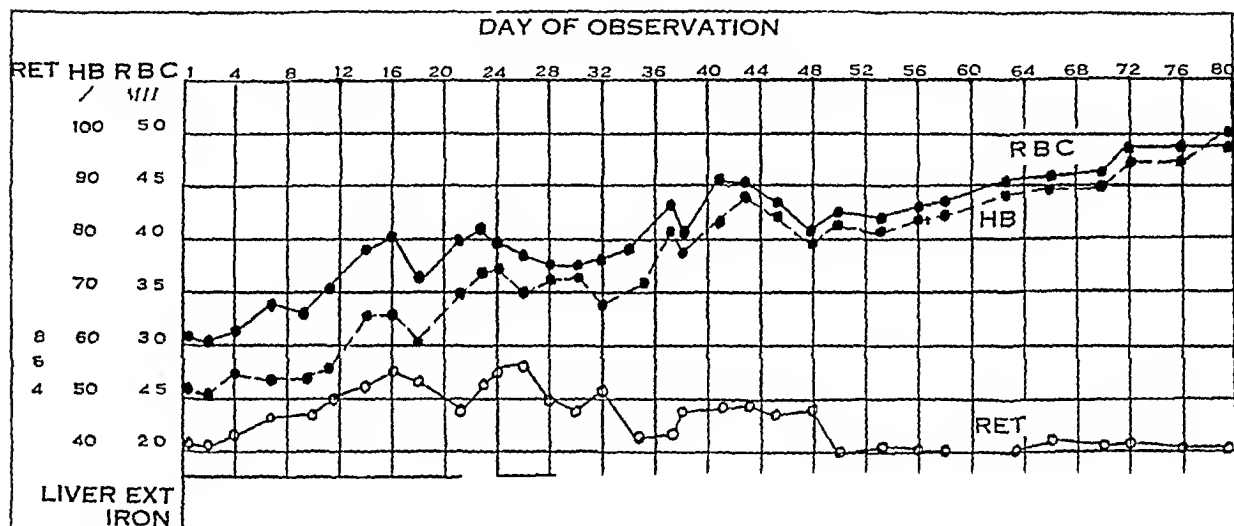


Fig 9 (case 5)—Chart of a patient with anemia associated with chronic dysentery, temporary gastric anacidity, a smooth tongue and signs of subacute combined sclerosis, who showed moderate improvement on a hospital diet and gradual recovery following the administration of liver extract and iron.

had always enjoyed excellent health. His usual diet consisted of rice, millet and corn. Occasionally he would take some mutton, but he did not eat any other kind of meat. Several weeks before entrance, the diarrhea increased, and the stools, which were liquid, contained mucus and some blood. He also began to notice pallor in his skin and swelling of his legs and face.

Examination—On examination, it was found that the patient was emaciated, pale and edematous. There was edema of the face, back, chest and legs. The eyes were normal, and there were no retinal hemorrhages. The mucous membranes were pale, and the tongue was normal in appearance. The heart and lungs were clear. The abdomen was moderately distended. The liver and spleen were not enlarged. The reflexes were present and active, and there were no sensory or motor disturbances. Sigmoidoscopic examination revealed numerous small ulcers in the lower part of the colon. *B. dysenteriae* of the Shiga type were recovered from scrapings of the ulcers. The urine was normal and did not

contain albumin. The stools were liquid and contained some mucus and red and white blood cells.

Examination of the blood showed 3,250,000 erythrocytes, 5,850 leukocytes and 65 per cent hemoglobin. The reticulocytes were 0.8 per cent. The cells appeared normal in size and shape. The average diameter of 500 red blood cells was 7.28 microns. The Price-Jones curve (curve C, fig. 12) showed essentially a normal curve, with a slight shift to the right. The Wassermann reaction of the blood was negative. Gastric analysis after injection of histamine showed a normal gastric acidity, with 42 per cent free acidity and 54 combined.

Course of Illness.—On rest in bed, hospital diet and iron therapy, the anemia showed little tendency to improve for a period of twenty-four days. During this time there was little improvement in the dysentery, and the patient was very ill. The reticulocytes, however, increased, and later there was gradual improvement of the anemia. The edema disappeared and the diarrhea improved. The patient gained weight and appeared quite normal. The changes in the blood are shown in figure 10.

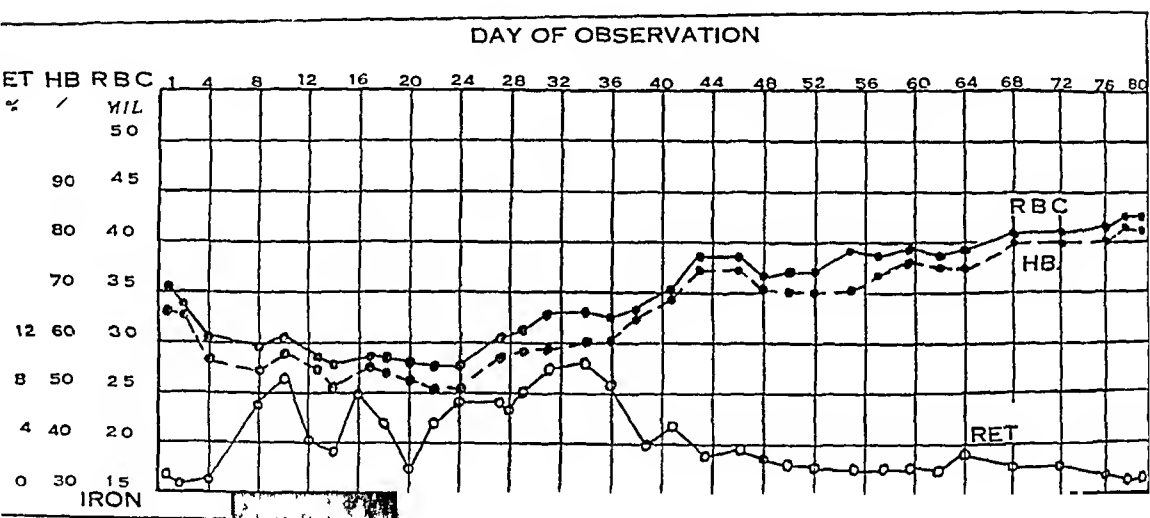


Fig. 10 (case 6).—Chart of a patient with anemia associated with chronic dysentery who recovered following treatment with iron.

COMMENT

These cases illustrate a number of interesting clinical features. We refer particularly to the anemia, the changes in the tongue, the gastric acidity and the state of the nervous system, together with conditions such as the deficiency disorders and the response of the anemia to treatment.

The salient clinical features in all the cases are summarized in table 1 and may be discussed in greater detail.

Changes in the Blood.—The most striking changes observed in the blood were those caused by anemia. Table 2 contains a summary of the main observations. The erythrocyte counts varied from 600,000 to 4,000,000 per cubic millimeter, and the hemoglobin from 15 to 70 per

cent The color index varied in the different cases between 0.6 and 1.25. The same hemoglobinometer and counting chamber were used in making these determinations, so that the color indexes in the different cases may be compared. The red blood cells varied in size and shape.

TABLE 1—*Summary of Clinical Data*

Case	Age	Sex	Duration of Dysentery	Diet of Patient Before Admission	Special Clinical Features				Comment
					Smooth Tongue	Gastric Anacidity	Changes in the Central Nervous System	Anemia	
1	22	M	2 mo	Bread, vegetables, flour	±	—	—	+	
2	22	M	4 mo	Wheat, rice, water, vegetables, no meat	—	—	—	—	Edema
3	42	M	1 yr	Millet, salted vegetable, no meat	±	—	+ Peripheral neuritis	+	Pellagra skin lesions
4	45	M	1 yr	General, meat, eggs, vegetables	+	+ Permanent	—	+	
5	46	M	6.8 yr relapsing	General Chinese diet	+	+ Temporary	— Subacute combined sclerosis	±	
6	18	M	2 mo	Rice, millet, corn, mutton occasionally	—	—	—	±	Edema
7	32	F	3 mo	Rice, millet, salt, vegetables	±	—	—	±	Pregnancy
8	24	M	14 mo	Rice, bread, millet, no meat	+	—	—	±	
9	25	M	3 mo	Millet, rarely meat and vegetables	—	—	+ Peripheral neuritis	±	
10	16	M	18 mo	Grain powder, millet, salted cabbage	—	—	—	—	
11	22	M	2 mo	?	—	—	—	+	
12	20	M	3 mo	?	—	—	—	—	
13	2	F	2 mo	Milk, rice, millet, vegetable, meat	—	?	—	±	Kerato malacia, edema
14	56	M	5 mo	General Chinese diet	±	+	+ Subacute combined sclerosis	±	
15	28	M	6 mo	Rice, wheat, millet, vegetables, meat occasionally	—	—	—	±	Edema
16	14	M	1 mo	Corn, millet, radish, soup, salt, vegetable, no meat	—	+	—	—	Edema

and their average diameter varied between 6.4 and 8.5 microns. Nucleated erythrocytes were seen occasionally.

One patient (case 14) was observed for only three weeks, and liver extract was given for only seven days. The response of the reticulo-

cytes was of interest. In a previous paper,⁵ two of us (C S K and C S Y) reported that the increase of reticulocytes in the blood of patients recovering from various forms of anemia was dependent on the severity and cause of the anemia as well as on the treatment employed. In this group, these cells varied from 0 to 8 per cent before treatment, increasing after treatment to between 2 and 38.6 per cent. Figure 11 illustrates in a general way that the lower the number of red blood corpuscles before treatment was begun, the greater was the

TABLE 2—Summary of Determinations of the Blood

Case	Red Blood Cells per Cc on Admission	Red Blood Cells per Cc on Discharge	Hemoglobin on Admission, per Cent	Hemoglobin on Discharge, per Cent	Reticulocytes		Color Index	Average Diameter of 500 Red Blood Cells, Microns	White Blood Cells per Cc	Type of Treatment
					Before Treatment, per Cent	After Treatment, per Cent				
1	600,000	4,000,000	15	85	1.0	38.6	1.00	6.40	4,350	Liver extract, iron
2	2,850,000	4,500,000	70	95	4.0		1.25	8.53	12,250	Hospital diet
3	2,000,000	5,000,000	35	85	0.30	6.0	0.8	6.61	2,200	Liver extract, liver, liver and iron
4	2,225,000	3,750,000	55	85	1.0	5.0	1.25		3,400	Liver extract, liver extract and iron, liver and iron
5	3,050,000	4,890,000	52	100	0.6	6.4	0.86	7.30	5,300	Liver extract, liver extract and iron
6	2,750,000	4,250,000	50	83	0.0	11.0	0.9	7.28	5,850	Iron
7	2,500,000	3,920,000	30	55	1.0	2.0	0.83		6,700	Blood transfusion
8	1,250,000	5,250,000	20	90	1.0	27.0	0.83	6.80	2,850	Hospital diet, cod liver oil
9	1,225,000	4,000,000	20	75	0.0	19.0	0.83	7.00	4,350	Hospital diet, cod liver oil
10	1,500,000	4,000,000	18	70	8.0	8.0	0.6	6.64	8,300	Blood transfusion, iron
11	2,800,000	4,730,000	51	89	3.0	8.6	0.9	7.00	11,000	Iron
12	1,000,000	3,700,000	25	78			1.2		6,000	Blood transfusion
13	4,000,000	5,000,000	45	85	0.2	14.4	0.6	7.15	6,000	Liver extract, liver powder, iron
14*	1,800,000	1,200,000	34	35	1.4	1.0	0.7	7.40	7,300	Liver extract
15	2,520,000	3,750,000	54	75	0.4	8.2	1.1	7.20	3,000	Liver ash, transfusion
16	1,125,000	4,250,000	14	90	0.2	26.6	0.6	6.65	10,000	Liver extract, iron

* Treated for only fourteen days

response of the reticulocytes at the peak of the rise. The curve that is inserted for comparison was taken from figure 2 of the paper by Minot, Murphy and Stetson,⁶ and shows the response of the reticulo-

5 Yang, C S, and Keefer, C S. The Response of the Reticulocytes in Secondary Anemia Following Various Forms of Treatment, *Arch Int Med* **45** 457 (March) 1930

6 Minot, G R, Murphy, W P, and Stetson, R P. The Response of the Reticulocytes to Liver Therapy, Particularly in Pernicious Anemia, *Am J M Sc* **175** 581, 1928

cytes at different levels of the erythrocytes in patients with pernicious anemia following the administration of 300 Gm of liver or kidney. This curve was chosen because when liver was given to our patients, it was given in amounts of 300 Gm or its equivalent in liver extract. We should like to emphasize that this response on recovery occurred following different forms of treatment and was not characteristic of any particular kind of therapy.

Variation in Size of Red Cells and Price-Jones Curves—When the diameter of the erythrocytes was measured, and the results plotted

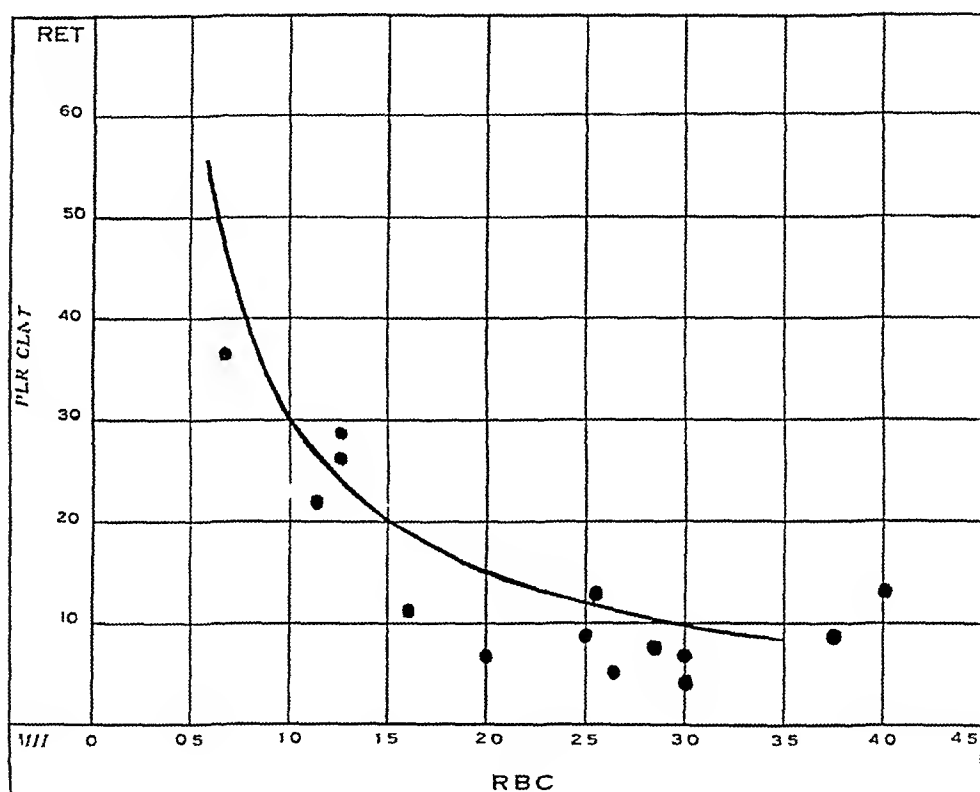


Fig 11—This chart illustrates the height of the reticulocyte response at different levels of erythrocytes during recovery. The curve which has been inserted was taken from figure 2 of the paper by Minot, Murphy and Stetson (*The Response of the Reticulocytes to Liver Therapy, Particularly in Pernicious Anemia*, *Am J M Sc* **175** 581, 1928), and represents the average response of the reticulocytes in patients with pernicious anemia following the administration of 300 Gm of liver a day. The reticulocyte response in our patients occurred regardless of the type of therapy employed.

according to the method of Price-Jones, it was found that three general groups existed: cells with an average diameter less than the normal, cells of normal diameter and those with a diameter larger than normal. In some cases there was a shift of the erythrocyte curve to the left of the normal curve (*D-E*, fig 12), in others the curve followed that of normal blood (*C-F*), and in others the curve shifted to the right (*B*).

In some, there was also a widening of the base of the curve. In figure 12 it may be seen that when the cells were smaller than normal before treatment, they approached the normal size during recovery. The same was true of the reaction of the large cells. It is noteworthy that these variations were wide, and no one type of reaction was observed. A few of the curves in which these differences may be observed have been plotted in figure 12.

Gastric Analysis—The results of the examination of the gastric juice following the injection of 0.5 mg of ergamine are summarized in

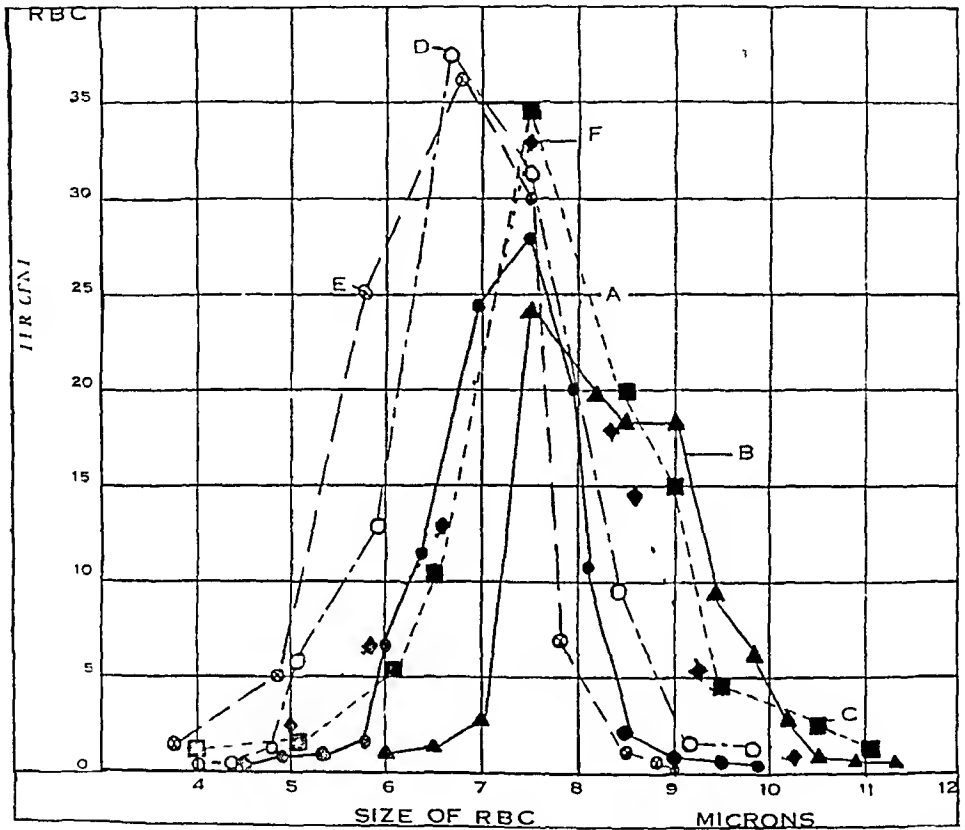


Fig. 12—Price-Jones curves of a few of the cases studied. Curve A is the normal curve, curve B is from case 2, C is from case 6, D is from case 13, E is from case 3 and F is from case 14.

table 3. Three patients had gastric anacidity. In two it was permanent, and in the other it was temporary. In the remainder, the gastric secretion was normal. These observations were of interest, since the relationship between alterations in gastric function and the development of anemia is of considerable importance in the study of all maladies associated with anemia, and it is necessary to have information of this kind in order to correlate the various features observed.

Atrophy of the Papillae of the Tongue—One of the outstanding clinical features that we observed in seven of these patients was atrophy

of the papillae of the anterior two thirds of the tongue. The natural history of the development of this condition is not known since it was an asymptomatic process in all but one patient. This patient had had recurrent attacks of glossitis and stomatitis and at the time of admission to the hospital he complained of pain during mastication. The tongue was large and smooth in the median part. The edges were quite red with prominence of a few of the papillae. There was no ulceration.

TABLE 3—*Summary of the Gastric Analyses Following the Histamine Test*

Case	Number of Observations	Free Acidity, Cubic Centimeter per Cent, Tenth Normal Hydrochloric Acid	Total Acidity, Cubic Centimeter per Cent, Tenth Normal Hydrochloric Acid
1	1	24	47
	2	52	64
2	1	38	59
	1	6	18
3	2	14	16
	3	38	46
	3	0	10
4	2	0	20
	3	0	14
	3	0	5
5	2	0	6
	3	2	16
	4	13	28
	5	16	55
	1	42	74
6	2	52	63
	1	12	26
7	1	26	32
	2	38	42
8	1	30	46
	1	67	75
9	1	14	27
	2	44	51
10	1	12	16
	1	0	6
11	2	0	6
	1	48	63
12	1	28	39
	1	28	39

but there was complete absence of the papillae in the central part of the tongue. In the other patients the degree of papillary atrophy varied from a complete absence of all of the papillae to an atrophy of those in the central part of the tongue. Within from eight to ten days after the patients were put on adequate diets the papillae began to reappear at first, at the edges of the tongue and later in the center. As the papillae became more prominent the normal grayish coating also reappeared. The atrophy of the papillae was not permanent in any of the patients observed. Photographs of the tongues of patients 9 and 4 are shown in figures 13 and 14.



FIG 13 (case 8) —Tongue of the patient *A* shows the complete atrophy of the papillae before treatment, and *B*, the normal appearance of the tongue following the patient's recovery



FIG 14 (case 5) —Tongue of the patient *A* shows the atrophy of the papillae before treatment, and *B*, the condition of the tongue following treatment

Changes in the Central Nervous System—In four of the patients studied, abnormal changes in the nervous system were demonstrated. In two, there was a peripheral neuritis, and in the others the signs of subacute combined sclerosis were present. In one of the latter patients, who was observed for a period of eighty days, the signs became less marked, but the signs of degeneration in the posterior column were still present on discharge from the hospital. The two patients with peripheral neuritis recovered completely.

Miscellaneous Associated Conditions—By associated conditions we refer to the edema that was present in six patients, keratomalacia in one, pellagra in one, hemorrhages in the ocular fundi in two and to changes in the skin, such as hyperkeratosis follicularis.

The diagnosis of "edema disease" was made on a basis of the presence of edema without other signs of cardiac insufficiency or renal disease and the presence of a low amount of serum protein in the blood. We observed a number of patients with this condition, in many instances not associated with anemia, in our experience, however, it has always been associated with a low, total serum albumin. This condition is a deficiency disorder due to a faulty diet, and it occurs frequently in patients with a disease process that interferes with normal nutrition.

Keratomalacia is seen not infrequently in patients with acute and chronic dysentery. This question has been discussed recently by Weech⁷ and Pillat.⁸ It is due to a lack of vitamin A and usually heals after administration of cod liver oil.

Pellagra has been observed and previously reported as a complication of dysentery. It usually appears after the dysentery has been present for a long time, and it responds to proper diet.

Hemorrhages into the retina in the absence of other hemorrhagic phenomena were observed twice. They occurred in patients who had severe anemia and disappeared following recovery. This observation is of interest, since it is usually stated that hemorrhages into the retina are fairly common in so-called pernicious anemia and uncommon in patients with other forms of anemia unassociated with hemorrhagic phenomena. It appears to us that hemorrhages depend somewhat on the severity of the anemia rather than on its cause, since we have also observed many retinal hemorrhages in patients with severe posthemorrhagic anemia due to bleeding hemorrhoids. This question requires further observation.

7 Weech, A. A. The Association of Keratomalacia with Other Deficiency Diseases, *Am J Dis Child* **39** 1153 (June) 1930.

8 Pillat, A. Does Keratomalacia Exist in Adults? *Arch Ophthalm* **2** 256 (Sept) 1929.

The lesions in the skin were of particular interest. We observed hyperkeratosis follicularis in three patients. These lesions are being studied in detail by Frazier and Hu,⁹ who will describe them in detail elsewhere. In most instances these lesions disappear following recovery from the malnutrition.

Response of Anemia to Treatment—The treatment employed in these patients varied considerably, depending on the patient's general

TABLE 4—Summary of the Patient's Response to Treatment

Case	Type of Treatment	Rate of	Reticuloocytes
		Hemoglobin Regeneration, per Cent a Day	Following Various Forms of Treatment, per Cent
1	Liver extract	22	38.4
	Iron	11	20
	Liver and iron	00	20
	Liver and iron	00	—
2	Hospital diet	03	40
3	Hospital diet	00	40
	Liver extract	10	50
	Liver	—	10
	Liver and iron	175	60
4	Hospital diet	00	40
	Liver extract	10	80
	Liver extract and iron	10	40
	Liver and iron	12	04
5	Hospital diet	10	60
	Liver extract	05	80
	Liver extract and iron	10	00
6	Iron	07	100
7	Blood transfusion	10	20
8	Hospital diet and cod liver oil	10	270
9	Hospital diet, cod liver oil	16	190
10	Blood transfusions, iron	05	80
11	Iron	05	86
12	Blood transfusions	10	—
13	Liver extract, liver powder and iron	10	144
14	Liver extract	00	10
15	Liver ash	10	80
16	Hospital diet	00	02
	Liver extract	05	50
	Iron	20	266

condition. A summary is given in table 4. Two were treated by transfusion of blood, one was allowed to recover spontaneously on a hospital diet and two were given an adequate diet supplemented with cod liver oil. To the other patients liver extract and liver and iron were given in various combinations.

In some of the cases described it was extremely difficult to draw conclusions regarding the merits of the particular form of therapy used. This was true because many of the patients showed a tendency

9 Frazier, C. N., and Hu, C. H. Personal communication to the authors.

to recover following an adequate diet. In some the recovery was slow and in others more rapid. This was not surprising, because it was only natural to suppose that if the anemia was the result of a faulty diet improvement would follow an adequate diet. However, when one attempts to determine the exact nature of the substances responsible for the recovery of these patients, the problem is extremely difficult since all of the essential substances necessary for hemoglobin synthesis are not known, and their distribution in the various food substances is incompletely understood. We felt that if we were able to show that regeneration of the hemoglobin could be accelerated by the addition to the diet of substances such as liver extract, liver or iron, which are known to be essential for the formation of hemoglobin, and if this was accompanied by an increase in the reticulocytes, we would be able to draw conclusions regarding the value of these substances. In analyzing the results with these points in mind, it is clear that no one particular kind of therapy was effective in producing acceleration of the regeneration of hemoglobin in all cases. In some liver extract was beneficial in others iron, and at times improvement followed the presence of both substances.

THE CAUSE OF THE ANEMIA

In considering the cause of the anemia in these patients our attention was directed to three factors: the disturbance in nutrition, hemorrhage from the intestine and infection.

The Disturbance in Nutrition—It was natural that our attention should be directed to the disturbance of nutrition in studying the cause of anemia in these patients, as they all showed a process that interfered with nutrition, and most of them had been on an inadequate diet before coming under observation. The anemia in some was associated with deficiency disorders such as keratomalacia, edema or pellagra. This idea gained further support when the anemia improved following an adequate diet, or after substances known to accelerate hemoglobin regeneration were added to the diet. This occurred in spite of the persistence of the infection and slight loss of blood in the stools.

In considering the factors that were responsible for the nutritional disturbance, the first of importance was the diarrhea. But since we found that only a certain number of patients with chronic diarrhea had anemia (fig. 1), it was difficult to explain all of the cases on this basis, and we felt therefore, that other factors were necessary for its development. In a previous paper¹⁰ two of us (C. S. K. and C. S. Y.) reported cases in which an inadequate diet was responsible for severe anemia and as a result of these observations the dietary habits of the patients

10 Keefe, C. S. and Yang, C. S. Anemia of Undernutrition. Report of Cases with Results of Treatment. *Nat. M. J. China* **15**: 701, 1929.

whose cases are presented in this paper were studied. When investigating the diets of patients with dysentery, it is of importance to determine the quality of the diet consumed before and after the onset of the diarrhea, because many patients who have been on adequate diets before the onset of dysentery consume totally inadequate diets after its development. In fact, the restricted dietary treatment of many patients with chronic dysentery often leads to the development of deficiency diseases. This question was discussed by Crohn,¹¹ who reported keratomalacia and anemia in patients who had been treated for chronic ulcerative colitis by a restricted diet. One need only recall the frequency with which deficiency disorders occur in patients with all forms of chronic diarrhea to be reminded of the importance of adequate nutrition in the treatment of these patients. It is not always clear, however, whether the inadequate diets begin before or after the onset of the illness, but from a study of our cases it appears that either may be the case.

Before we consider the diets of the patients whom we observed, it is well to recall the composition of the ordinary diets of the Chinese people. The recent studies of Wu and Wu¹² are of great importance in this connection. In an extensive survey of the foodstuffs contained in the ordinary diet of several groups of the so-called middle class Chinese in Peiping, they pointed out that while the diet of the average Chinese was adequate in fuel value it was suboptimal in proteins and vitamins A and D, probably adequate in vitamins B and C and low in calcium and phosphorus. The fat intake was low, and the carbohydrate consumption relatively high. They also presented evidence of the prevalence of deficiency diseases, and emphasized that there were probably many cases of mild deficiency that were not recognized. These facts also explain the frequent occurrence of deficiency disease in patients who have maladies that interfere with normal nutrition.

The diets of the patients whom we studied are summarized briefly in table 1. It was impossible to obtain information regarding the quantity of the various foodstuffs consumed, but it is readily seen that the quality of the food was below the average. In three of the patients (cases 4, 5 and 14), the diet was a general one and seemed adequate in fuel value. It was of interest to note that these patients had gastric anacidity. In one it was only temporary, while in the others it was permanent. It is likely, therefore, that this was a contributory factor in the development of the anemia. If the inadequate diets were responsible in part for the development of anemia, the correction of the diet should have been followed by an acceleration of the regeneration of the

11 Crohn, B. B. Ocular Lesions Complicating Ulcerative Colitis, *Am J M Sc* **169** 260, 1925.

12 Wu, Hsien, and Wu, D. Y. Study of Diets in Peking, *Chinese J Physiol*, Report Series no. 1, 1928, p. 135.

hemoglobin, and this we found to be the case in some instances. In others, improvement followed the administration of substances that accelerate the formation of hemoglobin, and this occurred in spite of the persistent diarrhea.

Hemorrhage—When anemia and ulceration of the intestine coexist, one naturally suspects that the loss of blood from the intestine is a contributory factor toward the anemia. In the patients under discussion, there was no history of a loss of a large amount of blood, and we never observed extensive hemorrhages. However, blood was found in the stools on microscopic examination, so that a certain amount of blood was lost in this way. The anemia that was present was out of proportion to the amount of blood lost, and improvement followed adequate treatment, in spite of the fact that blood continued to be present in the stools. It would seem, therefore, that the loss of blood from the intestinal tract was a contributory factor in the production of anemia but that it was not the essential one.

Infection—The importance of the dysentery in the production of anemia remains to be considered. Its relative importance is difficult to evaluate, except that the localization of the infection was such that it caused lesions that interfered with nutrition. As anemia was not present in all patients with chronic dysentery and since many patients improved in spite of the persistence of the infection, and we were unable to find any evidence of increased destruction of the blood, we felt that there was no evidence that the infection itself played an important part in the production of the anemia, in the sense of bacterial intoxication.

The anemia that was present in these patients was apparently due to disturbances in nutrition that were brought about by two principle factors: (1) a process that interfered with nutrition (diarrhea and intestinal ulceration) and (2) a faulty diet. Other contributory factors, such as hemorrhage from the intestine, infection or gastric anacidity, were of minor importance. These conclusions were supported by the fact that all of the patients had chronic diarrhea, which led to undernutrition, that most of them were on inadequate diets prior to admission to the hospital, that several had associated deficiency diseases, such as keratomalacia, pellagra and edema, and that the anemia tended to disappear when the patient was placed on a liberal diet supplemented by various substances known to accelerate the formation of hemoglobin. The increase in hemoglobin occurred in spite of the persistence of the infection and the loss of blood in the stools.

While the nature of the deficiency that was responsible for the anemia in these patients is unknown, we can state as a result of our observations that the deficiency was not the same in every case. There are good reasons why this should be so. In the first place, we wish to point out that when a diet is deficient in one substance, it is usually

deficient in others. The results of deficiency of single foods may be observed in animals after the diets have been carefully planned, but such conditions practically never exist in man. When studying patients with deficiency disorders it is not uncommon to find multiple deficiencies in the diet and their results in the same person. This was true of the patients studied. Moreover, the response of the patients to treatment indicated that no one form of therapy was effective in all. In some cases, liver extract was beneficial, whereas in others it was of no demonstrable value. In a few, iron was of distinct value, and in others its value was questionable. If we assume that both iron and other substances, such as the potent material in liver extract and liver, are necessary for the synthesis of hemoglobin and that a deficiency in either may result in anemia, it is not surprising that some cases of anemia respond to one and not to the other. From these facts, one might justifiably conclude that the anemia we observed was not always due to the same cause.

It also may be added that the nutritional disturbances in these patients were associated with factors that contributed to the anemia, namely, loss of blood and infection, and that these conditions may account in part for the irregular responses we observed.

In our present state of knowledge it is impossible to predict which form of therapy would be most effective in the treatment of these patients. Since the cause of the anemia seems to be different in the various cases and since we have no method available for recognizing these various deficiencies other than the response to treatment, additional information regarding these complex conditions must be collected before more definite conclusions can be reached.

RELATIONSHIP BETWEEN CLINICAL FEATURES OBSERVED IN THESE PATIENTS AND THOSE SEEN IN PERNICIOUS ANEMIA

The striking similarity between the clinical features observed in some of these patients and those seen in so-called pernicious anemia requires special comment. We refer to the changes in the tongue, the blood and the nervous system and the response that some of the patients showed following treatment with liver extract.

Changes in the Tongue—Atrophy of the papillae of the anterior two thirds of the tongue occurs in pernicious anemia, sprue, dysphagia associated with anemia¹³ in some patients with pellagra, infestation with hookworm and anemia¹⁴ and following partial gastrectomy.¹⁵ Aside

13 Cameron, J. A. M. Dysphagia and Anaemia, *Quart J Med* **22** 43, 1928.

14 Bahr, P. H. A Report on Researches on Sprue in Ceylon, 1912-1914, London, Cambridge University Press, 1915, p. 40.

15 Taylor, G. G., Hudson, R. V., Dodds, E. C., Warner, J. L., and Whitby, L. E. H. The Remote Results of Gastrectomy, *Brit J Surg* **15** 641, 1929.

from the cases described in this paper we have observed atrophy of the papillae of the tongue in patients with nutritional edema with and without anemia. This atrophy may occur with or without a preceding glossitis, and in most instances in which we have observed this condition it has been asymptomatic. It is a striking fact that during a remission in pernicious anemia the papillae may return, and the tongue then assumes a normal appearance. Our cases behaved in a similar manner. In two of our patients there was gastric anacidity, in one it was permanent, and in the other it was temporary. In others the gastric acidity was normal. It may be seen, therefore, that this condition of the tongue may occur with or without anemia and with or without gastric anacidity.

The exact significance of these changes in the tongue is difficult to appreciate. However, since similar changes are seen in conditions in which nutritional disturbances are common, it is not impossible that they are the result of dietary deficiencies. Cramer¹⁶ has shown that there may be extensive atrophy of the epithelial tissues of the intestinal canal when rats are fed on diets that are deficient in vitamin B, and these observations indicate that profound alterations may occur in the various epithelial tissues of the body following food deficiencies. That the changes described are the result of a food deficiency is suggested by the fact that they disappear following the correction of the diet. Whether this suggestion is true or not will require further observation and study. At the present time, it seems clear that if these changes are due to a deficiency in the diet, it is not the same deficiency that produces the anemia. This is suggested by our own observations and the course of events seen in pernicious anemia. In pernicious anemia the change in the tongue may occur before or on the appearance of the anemia. It may disappear following improvement in the anemia and then recur without the reappearance of the anemia. Whatever the cause of this striking clinical picture may be, it is of importance to note that changes in the tongue indistinguishable from those seen in so-called pernicious anemia occur in other conditions in which a faulty diet and anemia are present.

Changes in the Central Nervous System—Four of the patients had changes in the nervous system. Two had peripheral neuritis and two signs of subacute combined sclerosis. In one patient there was an improvement in the signs of disease of the posterolateral part of the spinal column following recovery from the anemia. The question has been raised frequently whether or not subacute combined degeneration occurs in any condition other than pernicious anemia, and particularly in the presence of other forms of anemia. There are two points of view, one which maintains that the disorder may occur in other forms of

16 Cramer W. On Vitamin Underfeeding, Brit J Exper Path 3:398, 1922.

anemia, and the other which denies that this disturbance occurs in any condition other than pernicious anemia. In other words, the use of the term subacute combined sclerosis should be limited to anemias, such as pernicious anemia and rare cases of hemolytic anemia. The latter view has been expressed most recently by Weil and Davison,¹⁷ who reached these conclusions from an extensive clinicomicroscopic study of the spinal cord in fatal cases in which the patients had had anemia in various forms. However, it must not be forgotten that these changes may be present before anemia appears, and in some patients the anemia may not be observed. Once these changes become established they may advance, remain stationary or improve. Furthermore, characteristic cases have been described in patients with anacidity associated with carcinoma of the stomach.¹⁸ Whether the symptoms and signs can be altered by placing the patient on a liver diet is a controversial point. This question was reviewed and discussed in a recent paper by Ungley and Suzman.¹⁹ They expressed the belief that liver was distinctly beneficial in causing the improvement of patients with subacute combined sclerosis. They also suggested that it was possible that this disease was a deficiency disorder occurring in persons with a constitutional diathesis, since achlorhydria and the presence of a hereditary factor is such a prominent feature in most cases. This is of considerable interest, since in the patients whom we observed there were achlorhydria and a nutritional disturbance, and in one patient, there was definite improvement following recovery from the anemia. It is obvious from one of the cases reported that signs of subacute combined sclerosis occur in patients with nutritional disturbance and without permanent achlorhydria.

The two patients who had peripheral neuritis were of considerable interest from the standpoint of etiologic diagnosis. We considered two possibilities—a toxic polyneuritis due to dysenteric infection and beriberi. It is well recognized that the dysentery bacillus of the Shiga variety produces an exotoxin that has an affinity for the nervous system and polyneuritis is occasionally observed in some patients with dysentery. However, it is difficult to decide in a given case whether the polyneuritis is due to the bacterial intoxication or is the result of a deficiency of the

17 Weil, Arthur, and Davison, C. Changes in the Spinal Cord in Anemia. A Clinicomicroscopic Study, *Arch Neurol & Psychol* **22** 966 (Nov.) 1929.

18 Waterfield, R. L. Addison's Anemia with Subacute Combined Degeneration of the Spinal Cord Secondary to Cancer of the Stomach, *Guy's Hosp Rep* **73** 208, 1923. Garvey, J. L., and Stern, L. D. Combined Sclerosis of the Spinal Cord and Carcinoma of the Stomach. Report of Case, *Am J M Sc* **168** 847, 1924.

19 Ungley, C. C., and Suzman, M. M. Subacute Combined Degeneration of the Cord. Symptomatology and Effects of Liver Therapy, *Brain* **52** 271, 1929.

antineuritic vitamin. Beriberi is frequently observed following dysentery, and has been commented on by Willcox,²⁰ Miura²¹ and others. It is important, therefore, to consider the possibility of beriberi in any patient with polyneuritis in whom there is a nutritional disturbance. It is also well to keep in mind that in some patients with anemia and signs of disease of the posterolateral part of the spinal column, there are coexisting signs of polyneuritis. Hamilton and Nixon²² demonstrated extensive changes in the peripheral nerves of patients with pernicious anemia and signs of involvement of the nervous system. They suggested that these changes probably account for some of the cases in which a considerable discrepancy existed between the physical signs and the pathologic changes in the spinal cord. Since changes in the peripheral nerves are known to follow deficient diets, and since they are found in patients with pernicious anemia and in those with anemia associated with dysentery when the diet is faulty, it is of importance to study this question further in order to determine the relationship between the changes in the nervous system and the previous diet of such patients.

Both of the patients whom we observed recovered completely. It should be remembered, however, that the recovery of these patients is quite slow even when adequate diets are supplied. The same is true of patients with the neuritic form of beriberi.

Changes in Gastric Secretion—Since Castle²³ demonstrated conclusively that gastric anacidity predisposes patients to the development of pernicious anemia, we have been interested in determining the state of gastric function in the patients whom we observed. In summarizing the results of gastric analysis, we stated that two patients had gastric anacidity of the permanent type and one had temporary anacidity, while the gastric secretion of the others was normal. It was noteworthy, however, that in the patients with anacidity and anemia, the diets were of a general character and adequate whereas the diets of the other patients

20 Willcox, W. H. Beriberi with Special Reference to Prophylaxis and Treatment, *Lancet* **1** 553, 1916.

21 Miura, K. Beriberi oder Kakke, *Ergebn d inn Med u Kinderh* **4** 280, 1909.

22 Hamilton, A. S., and Nixon, C. E. Sensory Changes in the Subacute Combined Degeneration of Pernicious Anemia, *Arch Neurol & Psychol* **6** 1 (July) 1921.

23 Castle, W. B. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. I. The Effect of the Administration to Patients with Pernicious Anemia of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, *Am J M Sc* **178** 748, 1929. Castle, William, and Townsend, W. C. II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Human Gastric Juice, *ibid*, p. 764.

were defective in quality. This suggests that a general diet may not protect a patient from anemia if he has anacidity and develops a pathologic process that interferes with nutrition. On the other hand, when the gastric secretion is normal and the diet is faulty and the patient develops a condition that interferes with nutrition, anemia may appear.

The relationship between the changes in gastric function and anemia is highly important. This question has been discussed recently by Castle,²³ Bloomfield and one of us (C S K),²⁴ and Chang and two of us (C S Y and C S K),²⁵ and the following facts are evident. There are a number of clinical conditions associated with anemia and a suppression of gastric acidity. In some cases, the gastric anacidity precedes and appears to predispose the patient to the development of anemia. Such examples as pernicious anemia, the anemia following the gastritis of chronic alcoholism, total gastrectomy, gastric polyposis, some cases of carcinoma of the stomach and the anemias associated with the temporary suppression of gastric acidity of unknown cause are cited in support of this idea. In other instances, gastric anacidity occurs during the course of an illness associated with anemia and may be only a contributory factor in increasing the anemia. In other words, in some cases gastric anacidity is of primary importance in predisposing patients to the development of anemia, whereas in others it plays only a secondary rôle. In our cases it was obvious that gastric anacidity was not responsible for the anemia observed, since in all but three the gastric secretion was normal. In the patients who had gastric anacidity, it was probably a contributory factor, since we pointed out that these were the only ones who had consumed a general diet.

What has been said regarding the relationship between the changes in the gastric acidity and anemia also applies to the changes in the nervous system and tongue. That is to say, in some cases gastric anacidity may be a predisposing factor for the development of these changes, and in others it may be only contributory.

This question requires further observation before the relative importance of each factor can be evaluated.

SUMMARY AND CONCLUSIONS

We have considered all of the clinical features that are said to be characteristic of pernicious anemia in a group of patients having chronic dysentery. These included atrophy of the lingual papillae, changes in the nervous system, gastric anacidity and an anemia that responded

24 Bloomfield, A. L., and Keefer, C. S. Gastric Acidity: Relation to Various Factors Such as Age and Physical Fitness, *J. Clin. Investigation* **5**: 285, 1928.

25 Chang, H. C., Yang, C. S., and Keefer, C. S. Improvement in Gastric Function in Patients Following Recovery from Secondary Anemia, *Nat. M. J., China* **15**: 752, 1929.

to liver extract therapy. It seems to us that it is of considerable importance that these conditions occur in a disorder in which nutritional disturbances are largely responsible. It is also noteworthy that they can occur without gastric anacidity. However, when a process that interferes with normal nutrition occurs in a patient with anacidity, a general diet may not protect him from the development of anemia. It is apparent from these observations that the features described were due to nutritional disturbances, and they support the hypothesis that similar features observed in so-called pernicious anemia are due to a deficiency disorder. In the light of our present knowledge it may be stated that the deficiency develops in patients with gastric anacidity because they are unable to obtain a sufficient amount of the essential substance or substances from a diet that contains only a small amount of the necessary material. On the other hand, when the diet is faulty and there is a process that interferes with normal nutrition, all of these features may appear when the gastric secretion is normal.

It may be recalled that this is not the first time that the characteristic features of pernicious anemia have been described as occurring in association with diseases of the intestinal tract, such as sprue, intestinal strictures, infestation with *Dibothriocephalus latus* and ulcerative colitis. As a matter of fact, the anemia associated with these conditions has been attributed to the intestinal lesions, and these cases have been used as an argument for the intestinal origin of pernicious anemia. At this time, we shall make no attempt to review the literature dealing with this question, but it is well to keep in mind that it has been clearly shown that patients with anemia associated with the conditions cited may respond to treatment with liver extract in the same manner as patients who have pernicious anemia. In the past, the general implication from the literature was to the effect that the anemia seen in these conditions is due to bacterial intoxication. In the future, these cases should be studied from the standpoint of nutritional disturbances in order to determine the relative importance of faulty diets and other nutritional factors in contributing to the development of anemia.

We have reported the results of a study of sixteen patients with anemia associated with chronic dysentery. The anemia varied in its morphologic characteristics and in its response to treatment. On the basis of our observations, we conclude that the cause of the anemia is not always the same, but the most important factors are the nutritional disturbances that result from faulty diet and a process that interferes with normal nutrition. In some patients, contributory factors, such as gastric anacidity, blood loss and infection, were of importance.

In the group as a whole, we observed all of the clinical features said to be characteristic of pernicious anemia. Some had similar morphologic changes in the blood, and the response of some patients to

treatment with liver extract was characteristic. Atrophy of the papillae of the tongue and changes in the nervous system were also observed. We attribute these changes to the nutritional disturbances, and we believe that these observations support the hypothesis that the various clinical features seen in pernicious anemia, such as papillary atrophy, changes in the nervous system, and the anemia, are due to a deficiency disorder.

ACUTE HEMATOPORPHYRIA

REPORT OF TWO CASES

V R MASON, M D

AND

R M FARNHAM, M D

LOS ANGELES

The essential symptom of the condition that Gunther¹ designated "hematoporphyrinuria" is the excretion of deeply pigmented urine the color of Burgundy wine containing an abnormal amount of hematoporphyrin. Two patients with the acute, idiopathic type of the disease were recently observed, and the histories are recorded in this article.

REPORT OF CASES

CASE 1—A white woman, aged 53, was admitted to the Los Angeles County General Hospital on Nov 7, 1929. The illness had begun a week previously with nausea, vomiting and cramplike pain in the lower part of the abdomen. During two days before admission the pain had been severe, and vomiting had been continuous. The pain was diffuse over the abdomen and radiated to the thighs. She had had no similar attack previously, and had never used sedative drugs. There had been no known exposure to lead. So far as she knew, no member of her family had been similarly affected. The past history was otherwise irrelevant.

Examination revealed a tall and slender woman. The skin was fair, with no areas of abnormal pigmentation. There was a small nodule, evidently an adenoma, in the right lobe of the thyroid gland. The lungs and heart were normal. The blood pressure was 160 systolic and 90 diastolic. The abdomen was soft and neither distended nor tender. The tendon reflexes were normal. No weakness of the muscles was present. The intern in the surgical service noted

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~ From the Medical Service of the Los Angeles County General Hospital.

1 In his first monograph, Gunther (*Die Hamatoporphyrinurie*, *Deutsches Archiv für klin. Med.* **105** 89, 1911) discussed hematoporphyrinuria as a symptom of diseased states and as the essential symptom of a rare constitutional disturbance. To the latter condition he gave the name "hematoporphyrinuria." Later research confirmed his belief that hematoporphyrin, as prepared by Hoppe-Seyler, played no part in the disease in human beings. Since the name "hematoporphyrin" had been appropriated by Hoppe-Seyler, it was unfortunate that the disease in man was designated "hematoporphyrinuria" instead of the more correct "porphyria." However, on account of priority, Garrod (*Inborn Errors of Metabolism*, London, Oxford Medical Publications, 1923, pp 136-163) accepted Gunther's terminology, and it seems wise to retain it. It should be clearly understood that hematoporphyrin refers to a distinct compound prepared by Hoppe-Seyler and that this pigment is not found in human disease. The pigments excreted by patients with hematoporphyrinuria are coproporphyrin and uroporphyrin.

that the urine was very dark, but routine examination presented nothing unusual. The leukocyte count was 17,500 with 95 per cent polymorphonuclear neutrophilic cells. A flat roentgenogram of the abdomen showed moderate dilatation of the entire colon, but nothing suggesting an obstruction was observed. The cerebrospinal fluid was normal. The Wassermann and Kahn reactions with serum were negative. The blood plasma showed nonprotein nitrogen, 58 mg and preformed creatinine, 13 mg per hundred cubic centimeters. The temperature varied between 100 and 102 F. The pulse rate varied between 80 and 120 per minute. The patient became delirious and noisy, and there were hallucinations of sight and hearing. At times, there were Cheyne-Stokes respirations. She was irrational for eight days, but thereafter recovery was rapid and complete. When first observed, the urine was very dark and red, and on three occasions it contained large amounts of hematoporphyrin, which was extracted by Garrod's method. Urobilin was also present in the urine. As the disease progressed, the urine gradually assumed a normal color, and hematoporphyrin could no longer be detected. Hematoporphyrin could not be identified in the feces, although this examination was not made until late in the course of the disease.

CASE 2—A white man, aged 36, was admitted to the hospital on Oct 3, 1929. He had always been in good health. There had been no exposure to known sources of lead poisoning, and he had not used hypnotic drugs. No member of his family was known to have passed dark-colored urine. The patient's wife stated that during the two months preceding his illness, she had noticed dark staining of his underwear by urine. Early in September, 1929, the patient had begun to complain of nervousness and pains in the arms and legs. These symptoms increased in intensity, and he consulted a physician. The patient was given salicylates and mild sedatives without relief. On October 3, he began to have severe abdominal cramps with radiation of the pain to the thighs. This was accompanied by constant vomiting. He had slight fever. The leukocyte count was 16,000 per cubic millimeter. Although the abdominal symptoms were atypical, they were so severe that an exploratory laparotomy was performed. The colon was found to be greatly distended, and a normal appendix was removed. Pain in the abdomen radiating to the arms, chest and thighs persisted, and morphine had to be administered repeatedly for relief. Slight fever was constantly present. On the thirteenth postoperative day, the abdominal cramps were again severe. A barium enema was given, and roentgenograms showed marked dilatation of the transverse and descending colon (fig 1). The patient was delirious at times. The face seemed slightly pigmented. There was a small nodule in the thyroid gland, apparently an adenoma. No abnormalities were noted on examination of the abdomen in spite of the severity of the symptoms. A tentative diagnosis of hematoporphyrinuria was made at this time, and a fresh specimen of urine was dark, almost black. (The clinical pathologist then recalled that a previous specimen was the same color, but assumed that it was dependent on the use of some silver salt.) When examined by Garrod's method, the urine gave the characteristic absorption spectrum of hematoporphyrin. It also contained urobilin in large amounts and other pigments, probably melanin and urofaecal. Even after the extraction of hematoporphyrin, the color of the urine was not appreciably altered. The leukocyte count varied from 13,000 to 16,000 per cubic millimeter. The spinal fluid was normal. The Wassermann reaction was negative with serum and spinal fluid. The amount of hematoporphyrin in the urine gradually diminished as the disease progressed. The plasma contained 115 mg of sugar, 13 mg of preformed creatinine, 151 mg of cholesterol and 105 mg of calcium per hundred cubic

centimeters, the carbon dioxide-combining power was 58 per cent by volume. On November 1, the patient was restless and irrational much of the time. He complained of severe pains in the extremities. All of the limbs were appreciably weak. Slight dysphagia and dysarthria developed, and he drooled saliva. He was soon delirious constantly, and apparently had auditory and visual hallucinations. The tendon reflexes diminished, and eventually disappeared. He gradually became comatose, and died with symptoms of bulbar paralysis, on November 10.

Autopsy—The body was that of a middle-aged white man, well developed, but only fairly well nourished. The skin was normal, except for brownish pigmen-



Fig 1 (case 2)—Roentgenogram after a barium enema, showing dilatation of the colon under the left leaf of the diaphragm.

tion of the face. There was a well healed abdominal incision. The thyroid contained a small cystic adenoma. The lungs were free in the pleural cavities. They were somewhat congested, and on section, a frank purulent bronchitis was seen. There was no evidence of pneumonic consolidation. The heart was normal. The abdominal viscera, including the pancreas and suprarenals, were essentially normal. Sections of the liver were stained by hematoxylin and eosin and also by methods to demonstrate the presence of iron. There was slight cloudy swelling. Many polygonal Kupfer cells contained large masses of brown pigment, usually amorphous, but rarely in crystals (fig 3). With a stain for iron about equal

portions of these deposits were iron-free and iron-containing pigments. There was no microscopic evidence of damage of the parenchyma of the liver other than cloudy swelling. The brain, spinal cord and sections of the brachial plexus were removed and hardened in a 10 per cent solution of formaldehyde. The gross morphology of these organs showed no alterations from the normal appearance save for cystlike spaces in the brain. These were evidently manifestations of postmortem activity of gas-forming organisms. Blocks of tissue from various portions of the brain and spinal cord and sections of the brachial plexus were

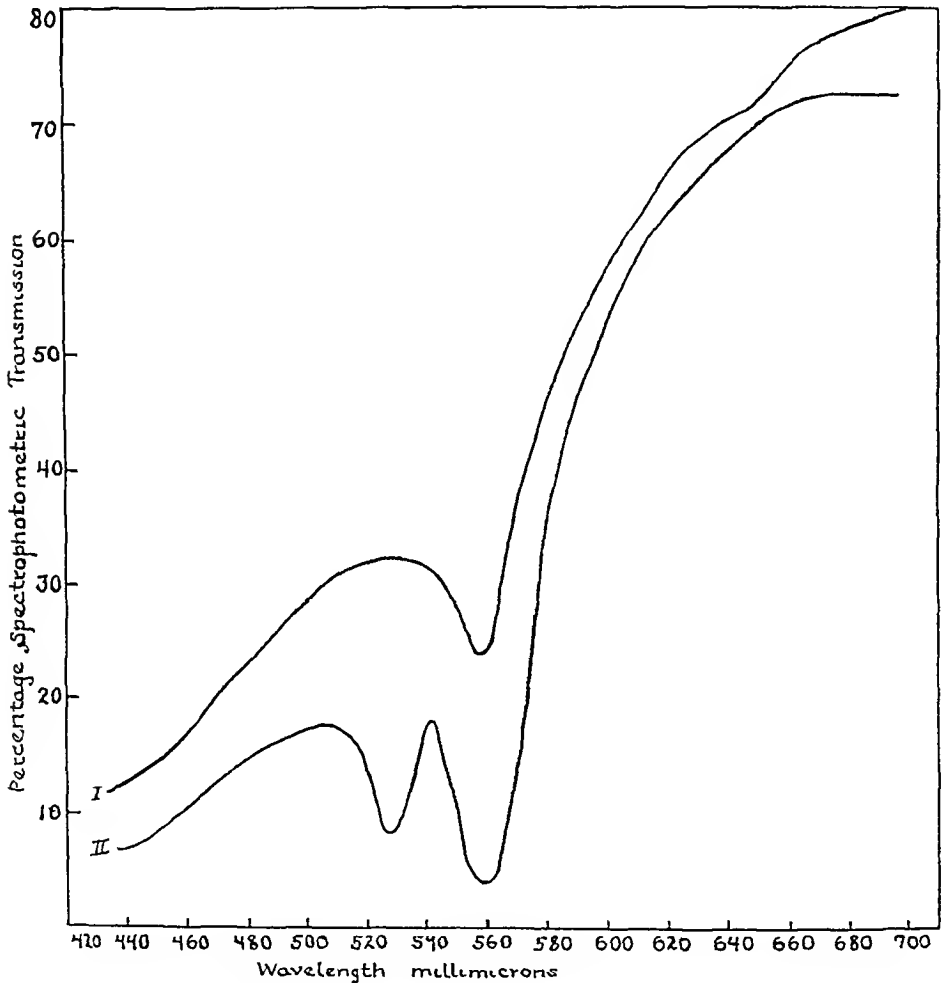


Fig 2—Spectrophotometric curves of transmission. Curve I, acid-alcohol solution of hematoporphyrin from urine of patient in case 1, curve II, acid-alcohol solution of hematoporphyrin from urine of patient in case 2. The maximal absorption was at 555 millimicrons. These curves were made by Dr Charles Sheard (Sheard and Goeckermann, *J Lab & Clin Med* **15** 162, 1929).

studied with the aid of the following methods: hematoxylin and eosin, van Gieson's method for connective tissue, Foot's method for reticulin, scharlach r and Nile blue for fat, Mallory's phosphotungstic acid-hematoxylin and aniline blue, Horta's silver carbonate and Cajal's gold sublimate methods for neuroglia, and Cajal's and Bielschowsky's methods for unmyelinated nerve fibers. In addition, the sections of the peripheral nerves were prepared by Marchi's method. There were no changes in the morphology of the nervous or supporting elements.

of the various portions of the brain investigated. In the spinal cord were found small areas of distortion and infiltration of wandering cells, confined apparently to the white commissure. The large motor cells of the anterior horn showed minor evidence of chromatolytic change, but this was neither constant nor characteristic.

Of particular interest was the evidence of a diffuse degeneration of moderate degree in all sections of the peripheral nerves as demonstrated by the Nile blue, the Scharlach R and the Marchi preparations. The process involved the fibers

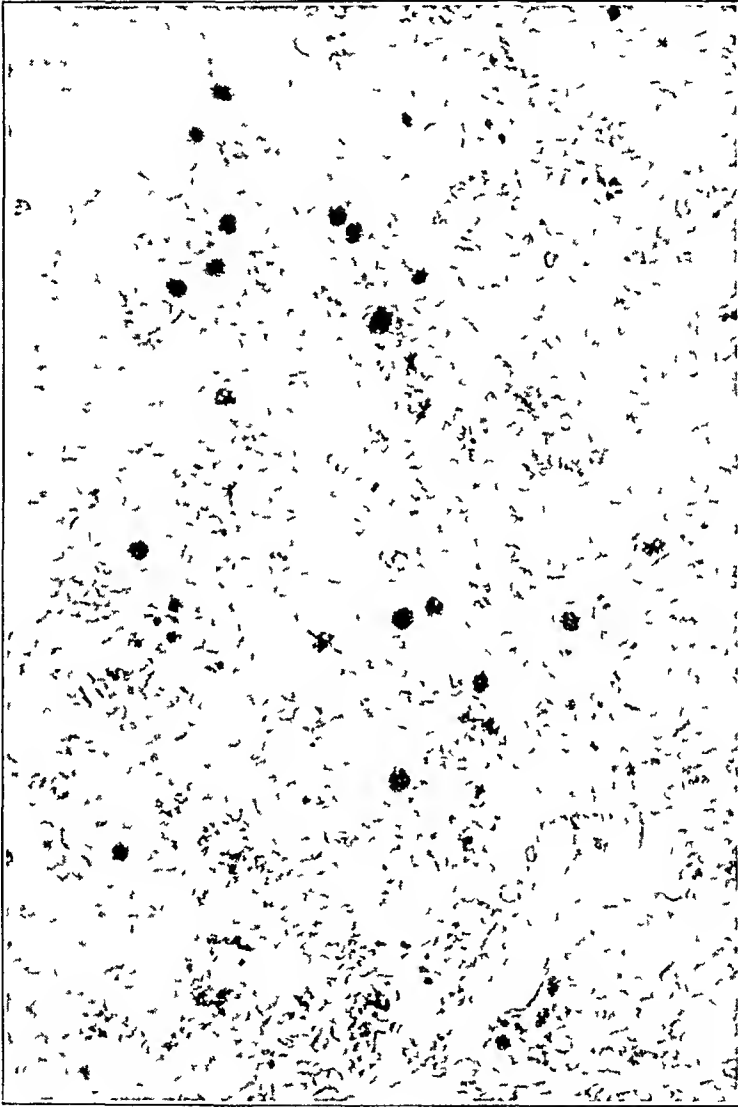


Fig. 3—Section of liver from case 2, showing stippled pigmentation of cells with iron-free pigment and large masses of iron-containing pigment.

uniformly throughout the extent of the section. Routine methods showed no accumulation of wandering cells or variation in the connective tissue elements of the nerve trunk. It is evident that the process was a true parenchymatous degeneration.

These two patients presented the characteristic symptoms of the acute or idiopathic type of hemato porphyria¹. There was no history of previous attacks or of a familial incidence of the disease. Furthermore,

plumbism and the use of sulphon-methane, barbitol or allied drugs could be excluded. The first symptoms resembled those of an acute surgical abdominal condition, and one patient had a laparotomy performed without relief. Each patient developed unusual nervous symptoms. In one, an ascending paralysis of peripheral nerve origin led to a fatal termination. In the other, the symptoms of a toxic psychosis developed, and recovery eventually took place.

PORPHYRINS

The porphyrins are a group of closely related pigments of considerable importance in the study of biologic reactions to light and of pigment metabolism. The name "hematoporphyrin" was first employed by Hoppe-Seyler to designate a pigment produced by the action of sulphuric acid on hematin. He described its chemical properties and also its complicated absorption spectrum. Subsequently, a similar compound was prepared from hemin crystals by Nencki. Since then a series of porphyrins have been prepared from myoglobin,² chlorophyll and other sources. For some time these artificial porphyrins, as well as the natural porphyrins encountered in the urine of normal and of diseased human beings, were believed to be identical. Fischer,³ however, was able to prepare pure methyl esters of some of the porphyrins. He showed that the porphyrin molecule contains four pyrrole rings, as pointed out by previous investigators, and that the various porphyrins differ in their content of carboxyl groups. It was possible, therefore, to gain some idea of the type of porphyrin present in disease by this method. Schumm⁴ also undertook the problem of the identification of the various porphyrins by means of accurate measurements of the absorption spectrums of the different porphyrins with the grating spectroscope. The result of these investigations was the demonstration that the porphyrins encountered in the excreta of normal and diseased human beings differ from the artificial porphyrins prepared by the methods of Hoppe-Seyler or Nencki. H. Fischer prepared pure methyl esters of the porphyrin excreted by Gunther's patient with con-

2 Gunther, H. Der Muskelfarbstoff, *Virchows Arch f path Anat* **230** 146, 1920.

3 Fischer, H. Ueber das Urinporphyrin, *Ztschr f physiol Chem* **95** 34, 1915, Ueber die Giftigkeit des Porphyrins, *ibid* **97** 109, 1916, Beobachtungen an frischem Harn und Kot von Porphyrinpatienten, *ibid* **97** 148 1916, Ueber die Konstitution des Kotporphyrins *ibid* **98** 14, 1916, Ueber die Konstitution des Urinporphyrins, *ibid* **98** 78, 1916.

4 Schumm, O. Ueber Hamatoporphyrin und Hamatoporphyrinogen aus Harn und uber das nach Nenckis Verfahren hergestellte Hamatoporphyrin, *Munchen med Wchnschr* **40** 1853 1913, Untersuchungen uber die Absorptionserscheinungen des Hamatoporphyrins und Mesoporphyrins im Gitterspektrum, *Ztschr f physiol Chem* **90** 1, 1914.

genital hematoporphyria and found that the porphyrin in the urine uroporphyrin, contained seven carboxyl groups and that the porphyrin in the feces, coproporphyrin contained three carboxyl groups. He was able, furthermore to convert coproporphyrin into uroporphyrin. Schumm,⁵ in a recent publication, stated his belief that the porphyrin in the urine from normal human beings is coproporphyrin, as is also the pigment in meconium and in the urine in instances of plumbism. In poisoning caused by sulpho-methane and barbitol and in acute hematoporphyria the porphyrin in the urine is uroporphyrin. In congenital hematoporphyria, coproporphyrin is present in the feces and uroporphyrin in the urine. Up to the present time, the porphyrins excreted in the urine and feces of patients with hematoporphyria have not been compared with each other in a sufficient number of cases for one to state with certainty whether identical porphyrins are always present in similar types of hematoporphyria in man.

The investigations of McMunn,⁶ Stokvis,⁷ Garrod,⁸ Neubauer⁹ and Gunther¹ proved that traces of porphyrin are present in urine, feces, meconium and bile from normal persons as well as in the excreta in many diseases. Under these conditions, the quantities excreted are minute. The absence of any simple quantitative method to determine the amount of porphyrin excreted has made it difficult to define the disease, and has led to confusion in diagnosis. An examination of the various studies made in reference to hematoporphyrinuria in general shows that porphyrin is a normal excretory product of human metabolism. Furthermore, the quantity of this pigment excreted in certain diseases may vary considerably. But even when its excretion is much more than normal, as in lead poisoning, typhoid fever, cirrhosis of the liver or melena, symptoms referable to the increase in pigment or comparable to those observed in hematoporphyria are absent. In his first report, Gunther attempted to define a state of porphyrism in which the patients were neurotic and under par, but he did not present the frank symptoms of hematoporphyria although abnormal quantities of porphyrin were excreted. This opinion has not been substantiated, although such a disease state is possible. Since up to the present time no examples of asymptomatic hematoporphyria have been recorded, it is

5 Schumm, O. Spektrochemische Untersuchungen an Porphyrinen, Porphyratinen und Muskelfarbstoffen, *Strahlentherapie* **28** 142, 1928, Ueber Hamatoporphyrine und Hamatoporphyrie, *Klin Wchnschr* **52** 1574, 1926

6 McMunn, cited by Garrod (footnote 1)

7 Stokvis, B. I. Zur Pathogenese der Hamatoporphyrinurie, *Ztschr f klin Med* **28** 1, 1895

8 Garrod, A. E. On the Occurrence and Detection of Haematoporphyrin in the Urine, *J Physiol* **13** 598, 1892

9 Neubauer cited by Garrod (footnote 1)

unwise to make a diagnosis of idiopathic hematopoiphyria unless a layer of urine 1 cm in thickness gives the definite absorption spectrum of porphyrin as Gunther suggested

Porphyrins produce a complicated and characteristic absorption spectrum that makes identification for clinical purposes simple and practically free from error. Many absorption spectra have been published, and accurate measurements of the alkaline and acid spectra have been made by Schumm and others and may be found in their articles. For clinical purposes, the method of Garrod¹ is very simple. The urinary phosphates are precipitated by alkali (10 per cent sodium hydroxide). They carry down with them about 80 per cent of the porphyrin present in the solution. The solution is filtered, and the precipitate is taken up by pouring hydrochloric acid-alcohol through the filter paper. The characteristic absorption spectrum of the acid porphyrin is easily identified.

CLINICAL FEATURES OF HEMATOPORPHYRIA

Gunther,¹ in 1911, published an extensive review of all the reported examples of hematoporphyria, and in 1922¹⁰ and 1925,¹¹ again brought the subject up to date. From the study of the scattered observations and from his own clinical material, he was able to demonstrate that the disease that he named "hematoporphyria" depended on a constitutional anomaly of metabolism, and was often familial and rarely hereditary in appearance. Garrod,¹ who had been one of the early investigators of the subject, accepted Gunther's views and placed the disease along with certain other "inborn errors of metabolism" in his monograph. The malady appears clinically in three types, to which Gunther gave the names hematoporphyria congenita, hematoporphyria acuta and hematoporphyria toxica. The clinical syndrome presented by patients of each group will be discussed briefly, together with abstracts of histories of the acute type reported since Gunther's latest review.

Hematoporphyria Congenita—In 1925, Gunther referred to eighteen examples of this type of the disease. Since that publication, case records have been published by Rothman,¹² Gray,¹³ Sato and Takahashi.¹⁴

10 Gunther, H. Die Bedeutung der Hamatoporphyrine in Physiologie und Pathologie, *Ergebn d allg Path u path Anat* **20** 607, 1922.

11 Gunther, H. *Hamatoporphyrin in die Krankheiten des Blutes und der blutbildenden Organe*, Berlin, Julius Springer, 1925, vol 2, p 622.

12 Rothman, P. E. Hematoporphyria. Report of Two Cases, *Am J Dis Child* **32** 219 (Aug) 1926.

13 Gray, A. M. H. Hematoporphyria Congenita with Hydroa Aestivale, *Proc Roy Soc Med* **17** 43, 1924.

14 Sato, A., and Takahashi, H. A New Form of Congenital Hematoporphyria. Oligochromemia Porphyrinuria (Megalosplastica Congenita), *Am J Dis Child* **32** 325 (Sept) 1926.

Toyama¹⁵ and Kitagawa¹⁶ Up to the present time, twenty-four proved examples of the disease are available for study

The disease is frequently familial, but only in the cases reported by Radaeli¹⁷ were a father and son affected The proportion of males to females is about 4:1 The disease may be present at birth¹⁴ although the first symptoms usually have not been noticed until months or even years later Of course, the chief symptom is the passage of Burgundy wine-colored urine containing abnormal amounts of porphyrin together with other unidentified pigments The symptom that often first calls attention to the disease is the development of a bullous eruption on the exposed surfaces of the skin by exposure to summer sunlight The efflorescence may be severe and lead to mutilation and scarring and to the development of changes resembling scleroderma Destruction of the ends of the fingers and the tips of the nose and ears may also occur In some instances, the teeth have been stained pink or brownish,¹⁸ and the bones may be deeply discolored by the pigment A few patients have presented hypertrichosis¹⁹ of the exposed parts Enlargement of the spleen has been frequent, and occasionally there has been some enlargement of the liver A moderate degree of secondary anemia has been noted often, and in a few instances this has been severe Increased fragility of the erythrocytes has not been described The leukocytes are usually normal, but in a few cases there has been a slight eosinophilia

Hydroa aestivale²⁰ has been known for many years and, in all, about one hundred cases have been recorded Hematoporphyria has been observed in approximately one fourth of these, and it is probable that the pigment, or perhaps its leukobase, might have been found more frequently if careful search had been made However, it is well known that hydroa aestivale may occur without hematoporphyria, and that in congenital hematoporphyria sensitivity to light may occasionally be absent

15 Toyama, J The Further Course of the Congenital Porphyrinuric Anaemia Previously Reported, *Jap J Dermat & Urol* **23** 440, 1923

16 Kitagawa, quoted by Hausmann, W, and Hauthausen, H Die Lichterkrankungen der Haut, Berlin, Urban & Schwarzenberg, 1929, pp 49-91

17 Radaeli, F Contributo alla conoscenza dell'hydroa vaccini-forme di Bazin, *Gior ital di dermat e sifil* **46** 93, 1911

18 Mackey, L, and Garrod, A E On Congenital Porphyrinuria Associated with Hydroa Aestivale and Pink Teeth, *Quart J Med* **15** 319, 1922, A Further Contribution to the Study of Congenital Porphyrinuria (Haematoporphyria Congenita), *ibid* **9** 357, 1926

19 Gray, A M H Haematoporphyria Congenita with Hydroa Vaccini-forme and Hirsuties, *Quart J Med* **19** 381, 1926

20 Hausmann, W, and Hauthausen, H Die Lichterkrankungen der Haut, Berlin, Urban & Schwarzenberg, 1929, pp 49-61

A review of the experiments on the photosensitizing properties of natural and artificial porphyrins does not lead to definite conclusions. Meyer-Betz,²¹ himself, received 0.2 Gm of hematopoorphyrin (Nencki) intravenously, and was sensitive to light waves that had penetrated glass (probably longer than gamma 313 millimicrons) and also to October sun rays and to Finsen light. He reacted with marked edema and superficial necrosis, lesions occurring comparable to those in animals sensitized to light, but not to hydroa in man.

Fraenkel,²² in an experimental study on animals, could not produce photosensitivity with the porphyrin from a patient with congenital hematopoiphyria in whom hydroa had never developed. Other observers either have failed or have succeeded in producing photosensitivity experimentally only after repeated experiments with careful control. Hausmann²³ stated that porphyrin may occur in two forms, one of which produces sensitivity to light and the other one of which does not. Fischer believed that the amount of coproporphyrin or its mother substance might be the determining factor, that is, when uroporphyrin is formed readily, the coproporphyrin is present only in small amount, and no sensitivity to light occurs. It seems probable that individual susceptibility, as well as the type of porphyrin present, may play some part in the problem. In general, the experimental evidence points to porphyrin as the cause of the photosensitivity, but just how this is brought about and just what form of the pigment is necessary is still unknown. The experiments to determine what region of the spectrum is most active in producing the hydroa are also not conclusive. In patients with hydroa aestivale, an eruption on the protected portions of the skin often cannot be produced or appears only after repeated exposures. The ultraviolet rays have been most active in the successful trials. In animals, visible rays near 500 millimicrons have been the most active. Furthermore, the intensity of the photosensitivity as determined experimentally by artificial light bears little relation to the severity of the eruption of the skin presented by the patient.

Hematopoiphyria Acuta—Gunther, in his article published in 1925, collected thirty-one cases that left no doubt concerning the diagnosis. In the past four or five years, the following reports have appeared

21 Meyer-Betz, F. Untersuchungen über die biologische (photodynamische) Wirkung des Hamatoporphyrins und anderer Derivate des Blut und Gallenfarbstoffes, *Deutsches Arch f klin Med* **112** 476, 1913.

22 Fraenkel, E. Experimentelles über Hamatoporphyrin, *Virchows Arch f path Anat* **248** 125, 1924.

23 Hausmann, W. Zur sensibilisierenden Wirkung der natürlichen Porphyrine, *Biochem Ztschr* **77** 268, 1916.

Langenskiöld²⁴ reported the case of a man, aged 51, who had complained of eructations of gas for a month. He had been well previously. Although a painter, the patient presented no symptoms referable to lead. On February 17, he had anorexia and severe abdominal cramps. On February 18, 19 and 20, the cramps continued, and there was slight jaundice. The urine was dark red. On February 21, he vomited foul-smelling material. There was marked tympanites. There was slight icterus, but no other pigmentation. The pulse rate was 100. There was no fever. The abdomen was soft, but some tenderness was present in the hypogastrium. There was no visible peristalsis. The dullness of the liver was normal. The urine was deep red, and contained urobilin and hematoporphyrin. The leukocyte count was 12,880 per cubic millimeter. The patient gradually recovered.

In the case reported by van der zoo de Jong,²⁵ severe abdominal pain, with vomiting and constipation developed in a woman, aged 26, without significant family or past history. The urine was dark brown, and contained hematoporphyrin and melanin. The patient recovered.

Melkersson²⁶ reported the case of a woman, aged 28, with no family history of the disease and no evidence of lead poisoning or of the use of hypnotics, who became ill in 1922 with violent epigastric pain and chills. She vomited constantly. The abdomen was tender. The urine was reddish brown. She improved rapidly and was apparently well in two weeks. In 1923, she had a similar attack with pains in the arms in addition to the previous symptoms. In January, 1924, she had another attack. In December, 1924, she became ill with fever, chills, severe epigastric pain and constant nausea. There were visible coils of small intestine (presumably). There were 13,000 leukocytes per cubic millimeter. The urine contained urobilin and hematoporphyrin. The fragility of the erythrocytes was normal. Evidences of peripheral neuritis with severe bulbar symptoms and incontinence developed, but by April 21, 1925, she had recovered completely.

Kuntzen and Becker²⁷ reported the case of a man, aged 59, with an irrelevant family and personal history, who had severe attacks of colic and had lost 20 pounds (9 Kg) in three months. The liver was rather large, the sclerae were slightly brown. The patient said that his skin tanned easily. The leukocyte count was 5,200. The urine contained urobilin. A diagnosis of pericholecystitis was made, and the abdomen was explored. Slight cirrhosis of the liver was found. The colic continued, and the urine was deep Bergundy red and contained hematoporphyrin. The colic continued intermittently for the next three months. The patient lost weight. A roentgenogram showed wide dilatation of the duodenum. A second operation was performed, and a carcinoma of the pancreas was found. At autopsy there was cirrhosis of the liver with hemochromatosis and a carcinoma of the pancreas.

24 Langenskiöld, F. Om hematoporfyrin med ileusliknande symtom, *Finska lak-sällsk. handl.* **70** 241, 1928.

25 van der zoo de Jong, H. H. Een Waarschuwing by Het Zocken Naar Melanine en Haematoporphyrine in de Urine, *Nederl. tijdschr. v. geneesk.* **69** 598, 1925.

26 Melkersson, E. Un cas de porphyrie aigue spontanée avec symptomes nerveux et un brève revue de la question des porphyries, *Acta med. Scandinav.* **63** 153, 1926.

27 Kuntzen, H., and Becker, R. Ueber akute Hamatoporphyrinurie und symptomatische Hamatoporphyrinurie, *Deutsche Ztschr. f. Chir.* **206** 332 1927.

Weisz²⁸ reported a case in a woman, aged 27, who stated that six siblings died in infancy with abdominal cramps. She had had several attacks of severe abdominal pain with vomiting. During the attack reported the epigastrium was tender, the liver was soft and extended below the umbilicus, and the spleen was not felt. The leukocyte count was 12,000. The fragility test of erythrocytes gave normal results. The urine was reddish brown and contained urobilin and much hematoporphyrin. Cystin crystals were found. During another attack porphyrin was found in urine and stools. The duodenum was markedly dilated, and the face appeared pigmented. Considerable anemia developed. During a subsequent attack the colon was greatly distended. An ascending neuritis developed that caused death. At autopsy, no remarkable features were present. The liver was normal.

Beilm²⁹ reported the case of a man, aged 24, who entered the clinic on account of weakness of the right leg and arm and pain in the cervical region and the right side of the chest. There were constipation, vomiting, pain in the lower part of the abdomen and headache. The urine was deep red and contained hematoporphyrin. The spinal fluid was xanthochromic, and contained 152 cells. The symptoms progressed, and after three weeks uremia-like attacks occurred with increased excretion of hematoporphyrin. The patient died of asphyxia after characteristic symptoms of a Landry's paralysis had appeared.

Moen³⁰ described the case of a man, aged 29, who was observed for gallstones on Sept 1, 1925. The past history and family history were irrelevant. The patient complained of sleeplessness, headaches and paresthesias over the body. He had taken some bromides, but no other sedatives. The urine had been of portwine color for six months. For three days before admission, he had been very ill with sore throat. He was constipated. He grew worse, and developed severe abdominal pain, especially in the flanks. He vomited bile-stained fluid. The abdomen was tympanic. The urine contained hematoporphyrin but not urobilin, it was deep red. The patient had severe pain in the legs and arms, but eventually recovered. On Feb 8, 1928, the same symptoms appeared. The urine contained hematoporphyrin and urobilin. A similar attack occurred three weeks later.

Rothman¹² reported a case in a colored boy, aged 13 years, who complained of pains in the abdomen and in the legs. His mother noticed that the urine was red. About a week later the symptoms disappeared, returning on Aug 22, 1924. He had slight fever. On physical examination no abnormalities were observed. The leukocyte count was 16,500. The urine was brown and contained albumin and casts. The Wassermann reaction was negative. The brown color disappeared from the urine and the patient recovered. A similar attack appeared on Jan 22, 1925. The patient died suddenly two days later. At necropsy, all of the viscera were darkly colored, the spleen weighed 220 Gm, the capillaries of the liver were filled with erythrocytes, the bone-marrow was hyperplastic, and no alterations of the peripheral nerves were found. The urine from the bladder contained hematoporphyrin.

28 Weisz, H. Zur Kenntnis der Porphyrinkrankheiten, *Deutsches Arch f klin Med* **149** 255, 1925.

29 Beilm, I. A. Das Landrysche Syndrom mit Hamatoporphyrinurie, *Russk klin* **10** 161, 1928.

30 Moen, E. Et tilfelle av haematoporfyri, *Norsk mag f lægevidensk* **89** 778, 1928.

Up to the present time, about forty-one examples of the acute, idiopathic type of the disease are available for study. It is probable that occasionally the condition has gone unrecognized and that the records of some patients with the disease have not been reported. It is true, however, that the malady is rare.

The disease is occasionally congenital,³¹ although no hereditary occurrence has been recorded. Symptoms most frequently appear in the third and fourth decade, but exceptions have been noted. The condition occurs in females slightly more frequently than in males.

The clinical syndrome presented by the patients has been similar in all instances. The first definite symptom is usually severe, cramplike abdominal pain between the umbilicus and the pubis at times radiating to the flanks or the thighs or even to the chest. Not infrequently, this symptom is preceded by weeks or even months of ill health with complaints of weakness, nervousness, sleeplessness and vague pain in the abdomen or extremities. With the onset of severe abdominal cramps, nausea and vomiting appear and become constant. Constipation is practically always present. There is often slight fever and moderate leukocytosis. Urinary symptoms, usually strangury, often occur. The abdomen is usually soft, but may be slightly tender over the hypogastrium. Visible peristalsis has rarely been observed. Roentgenograms have often revealed dilatation of the duodenum, the ileum or some portion of the large bowel. These observations have occasionally been confirmed at operation. In one instance, all of the intestines were greatly contracted. General physical examination usually gives normal results. At the onset of the symptoms the urine is deep red and contains urobilin, porphyrin and occasionally other pigments. As the symptoms of the attack ameliorate, the color of the urine promptly returns to normal, although porphyrin may be present for some time. A history of recovery from several similar attacks is not unusual.

In the attacks that end fatally, symptoms from the nervous system appear early. These consist of toxic-delirious states, occasionally with convulsions, or of weakness of the extremities, often preceding the development of an acute ascending paralysis ending with an acute bulbar palsy and asphyxia.

The mechanism of the production of these symptoms is still in doubt. As Snapper suggested, it seems probable that the abdominal phenomena are caused by alteration of function of the nervous system. Whether this damage is produced by porphyrin or by some other substance formed during the course of the anomaly of pigment metabolism is also obscure.

31 Barker, L. F., and Estes, W. L., Jr. Family Hematoporphyrinuria and Its Association with Chronic Gastroduodenal Dilatation, Peculiar Fits and Acute Polyneuritis. *J. A. M. A.* **59** 718 (Aug. 31) 1912.

Pathologic alterations of the organs other than the nervous system are inconspicuous. The viscera may be congested. The spleen and liver may be slightly enlarged. The liver often contains pigments.

During the attack the urine may be almost black, and its color is little altered even after the removal of the porphyrin. Melanin, skatole, tyrosine, leucine, urofuscine and other unidentified pigments have been found in the urine. Their significance will be discussed later.

Hematoporphyrina Toxicæ—In this group, Gunther placed the reported examples of genuine hematoporphyrina following the administration of sulphon-methane, barbitol and allied drugs. There is no proof that drugs cause the disease, except in patients with latent hematoporphyrina. The symptomatology is identical with that presented by patients with acute hematoporphyrina. Sensitivity of the skin to light has been recorded once following the excessive use of phenobarbital.

COMMENT

Hematoporphyrina may be considered an independent disease of pigment metabolism due to some constitutional defect. It may be present at birth or may appear first at any age. The varying symptomatology of the congenital and acute types of the disease is probably more apparent than real, although not enough evidence is at hand to make positive assertions at present. Why neurologic disturbances are present in some instances and photosensitivity in others and only the excretion of porphyrin in still others cannot yet be explained. It seems safe to assume that the two porphyrins, uroporphyrin and coproporphyrin, are the same in all instances of hematoporphyrina, and that the varying symptomatology is dependent on the degree of the constitutional factor and the susceptibility of the patient to the disease.

The excreta of normal persons contains porphyrin in minute quantities, as previously mentioned, and it may be looked on as a normal product of metabolism. The amount secreted in certain disease states may be increased considerably above normal. In such instances the characteristic symptoms associated with hematoporphyrina are lacking. An exception must be made in the cases of intoxication with sulphon-methane, barbitol and allied drugs. But, as Gunther has stated, even in these cases it may be possible that the patients have the constitutional defect in a latent form that is activated by the drug.

The place of origin and the mother substance of hematoporphyrin are unknown. All of the porphyrins are so similar in composition that it might be possible for the body to convert one into another. If this is possible, porphyrin could arise from chlorophyll or from endogenous or exogenous hemoglobin or myoglobin. It might arise during the process of anabolism or catabolism of myoglobin or hemoglobin or from

some perversion of the formation of bile or derangement of function of the liver. In attempts to elucidate the pathogenesis of the disease, many theories have been propounded of which only a few deserve consideration. The assumption that retention of the pigment by the kidney might lead to porphyrin intoxication without increased formation of the pigment would be tenable in the cases reported by Harbitz,³² and by Melkersson.³³ It is not probable in other reported cases. The theory of the origin of the pigment from ingested chlorophyll or hemoglobin or myoglobin may be easily disproved by feeding experiments with congenital porphyritic patients. The absence of evidence of hemolysis or of the development of marked anemia excludes destruction of blood and liberation of hemoglobin as necessary preliminaries for the formation of excessive amounts of hematoporphyrin. The two remaining possibilities namely, that the disease is dependent on disturbed liver function and bile metabolism or on defective hemoglobin synthesis, are deserving of more serious consideration.

Theories but not satisfactory proof of damage of the liver have been presented, and a review of all of the autopsy records does not substantiate this point of view. Furthermore, those patients with the congenital type of this disease and those who recover from an acute attack show no evidence of hepatic disease or of biliary disease. The liver of our patient (fig 3) showed evidence of cloudy swelling, and the parenchymatous and Kupffer cells contained large amounts of non-containing and iron-free pigment. We believe that these alterations are the result and not the cause of the disease. The constant presence of urobilin in the urine in attacks of acute hematoporphyria is difficult to explain, but we believe that it should be related to temporary damage of the liver or possibly to disturbance in the bone-marrow.

Recent work by Fischer, Schumm, Borst, Konigsdorff³⁴ and Fraenkel has produced evidence that more nearly fits the known facts. Fraenkel, Hegler and Schumm³⁵ sectioned the body of a patient with congenital hematoporphyria, and found porphyrin in the bones and non-free and non-containing pigment in the spleen, Kupffer cells and erythro-

32 Harbitz, F. Hematoporphyrinuria as an Independent Disease (Hematoporphyria) and as a Symptom of Liver Disease and Intoxications, *Arch Int Med* **33** 632 (May) 1924.

33 Melkersson (footnote 26) Rouillard, J. La porphyrinurie, *Presse med* **34** 1061, 1926.

34 Borst, M. Untersuchungen über kongenitale Porphyrin, *Verhandl d deutsch path Gesellsch* **23** 353, 1928.

35 Konigsdorff, H. Zur Kenntnis der Porphyrin, *Strahlentherapie* **28** 132, 1928.

36 Fraenkel, E., Hegler, C., and Schumm, O. Zur Lehre von der Haematoporphyria congenita, *Deutsche med Wchnschr* **39** 842 1913.

blasts. The latter also contained porphyrin. Borst, with Königsdorffer and Fischer, had the opportunity to section the body of Matthias Petry.³⁷ The bones were pigmented. The marrow was deep red. The liver was large. The liver, lymph glands, kidneys and pancreas were pigmented. Ten different pigments were identified in the lymph glands, spleen, bone-marrow, liver, pancreas, stomach, intestine, kidneys, suprarenals, thyroid, hypophysis, testes, lungs, muscles, nervous system, choroid plexus and teeth. Some were crystalline and some amorphous. A few of them were lipid. Some were iron-free and others contained iron. The pigments were present in connective tissue cells, and in the endothelial epithelial and reticular cells. The bone-marrow contained many plasma cells and many macrophages that had devoured large numbers of erythroblasts. Microspectroscopic studies showed large amounts of porphyrin in these cells, together with hemosiderin and hematin. They believe that the erythroblasts in early embryonic life build up hemoglobin through the formation of porphyrin. In later embryonic life this is no longer true. The bone-marrow and spleen of Petry contained large numbers of erythroblasts filled with porphyrin, and the large phagocytic cells of the bone-marrow were loaded with fluorescent porphyrin-containing erythroblasts. In this instance a pathologic persistence of embryologic hemoglobin metabolism was present.

This theory perhaps more nearly meets all the requirements than any so far proposed. Assuming its validity, the primary defect is in the synthesis of hemoglobin. The remaining alterations are of secondary nature depending on the toxicity of the pigments liberated by the phagocytic activity of the macrophages.

The urine of patients with hematoporphyrina contains large quantities of pigment other than porphyrin, as do many of the organs. Melanin, skatole and urofaecin have been found, and urobilin is constantly present. Besides these there are other unidentified pigments. Their significance is not known, but a review of the reported cases indicates that they may play a determining rôle in the symptomatology. In the chronic congenital cases, these pigments are present in small amounts in the urine, while porphyrin is present in large quantities over long periods of time. Except for hydia, however, the patients are relatively symptom-free. In the reported cases of the acute types of the disease, the symptoms are severe when the urine is heavily pigmented with substances in addition to porphyrin, and as recovery takes place the amount of porphyrin diminishes but little, while the other pigments practically

37 Gunther (footnote 1) Borst, M., and Königsdorffer, H. Untersuchungen über Porphyrie, Leipzig, S. Hirzel, 1929.

disappear. Satisfactory investigation of these accessory pigments has not been reported to our knowledge, although they must be of considerable importance.

No satisfactory method for treating the acute cases has been devised. It has been suggested that calcium might be of value, but records of its use are not available. Treatment for *hydia aestivale* is more satisfactory, and consists of avoiding the direct rays of the sun. Gaird used a paste containing quinine that filters out the more destructive rays.

CONGENITAL HEART DISEASE

MEASUREMENTS OF THE CIRCULATION *

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CLINICAL AND EXPERIMENTAL DATA

The cyanosis of congenital heart disease is usually associated with a considerable degree of unsaturation of the arterial blood. In these cases, as noted by Lundsgaard and Van Slyke,¹ either (*a*) the blood that passes through the lungs is insufficiently saturated with oxygen, owing to some pulmonary defect, or (*b*) there is a shunting of some venous blood from the right side of the heart into the systemic aorta without its having passed through the pulmonary alveoli.

Some years ago Haldane and Douglas² placed a patient with cyanotic congenital heart disease in an atmosphere high in oxygen and noted that the cyanosis did not clear, they inferred that the defective aeration of the blood was not due to pulmonary insufficiency. On the other hand, Campbell, Hunt and Poulton³ tried the same procedure with one of their patients having congenital heart disease, and found that the arterial saturation of oxygen increased from 67 to 91 per cent. They inferred that in part, at least, the cyanosis in this case was on a pulmonary basis.

On the assumption that blood is shunted from the right side of the heart to the left, various calculations⁴ have been attempted to determine the amount of this shunting. In a series of three carefully studied cases, Dautrebande, Marshall and Meakins⁵ recently made several

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1 Lundsgaard, C, and Van Slyke, D D. Cyanosis, *Medicine* **2** 1, 1923

2 Haldane, J S, and Douglas, C G, quoted in Haldane, J S. Respiration, New Haven, Conn., Yale University Press, 1922

3 Campbell, J M H, Hunt, G H, and Poulton, E P. Breathlessness and Cyanosis, *J Path & Bact* **26** 234, 1923

4 Abbott, M E, in Osler and McCrae. System of Medicine, Philadelphia, Lea & Febiger, 1927, vol 4, p 612. Abbott M E, and Dawson, W T. Clinical Classification of Congenital Heart Disease, *Internat Clin* **4** 156, 1924. Raab, W, Weiss, R, Lowbeer, B, and Rühl, J. Untersuchungen über ein Fall von kongenitalen Herzvitium, *Wien Arch f inn Med* **7** 367, 1924

5 Dautrebande, L, Marshall, W R, and Meakins, J C. Studies of the Circulation in Three Cases of Morbus Caeruleus, *J Clin Investigation* **8** 123, 1929

calculations of this sort, but the results were so divergent as to lead them necessarily to the conclusion that the amount of the shunt, if present, could not be determined with the data and methods available.

The present investigation is a further effort to determine, by measurements of the blood and respired gases, the mechanism of the circulation in a case of congenital heart disease. These studies were made at several different times, both during the patient's stay of three weeks in the ward and during a three day period in a Barach oxygen chamber, with the atmospheric oxygen at from 44 to 46 per cent.

REPORT OF CASE

History—A S, an American girl, aged 12, was admitted to the service of Dr. Randolph West on March 7, 1930. According to her mother, she had been a normal child up to the age of 3, when she had an attack of fever and pain in the joints lasting several months. After this it was noticed that she soon became dyspneic on exertion, her skin turned bluish and her lips black. Ever since that time, the cyanosis and dyspnea had persisted, and she had recurrent attacks of joint pains, with swelling and redness, especially of the ankles. Her fingers had been markedly clubbed for at least five years. It had been observed that the cyanosis became worse in cold weather, the effect of exertion was not noted. She had swelling of the ankles whenever she was up on her feet.

Physical Examination—Examination showed a small, thin girl (154 cm in height and weighing 35 Kg) lying quietly in bed, breathing deeply and somewhat rapidly, but in no apparent respiratory distress. There was extreme cyanosis of the skin and mucous membranes, her lips and tongue were almost black. The fingers and toes were clubbed. The chest was deep and voluminous for her size, with good expansion of the lungs. The lungs were clear. The heart was moderately enlarged, the borders extending 3 cm to the right and 10 cm to the left. There were systolic shock at the apex and thrill over the third and fourth left interspaces. The first sound at the apex was soft, preceded by a mid-diastolic murmur, and followed by a systolic blow. At the base of the heart to and from murmurs were heard to the left of the sternum in the second and third spaces, the systolic murmur was transmitted toward the left clavicle. The second pulmonary sound was sharply accentuated. The liver and spleen were not felt.

The blood count showed red blood cells, 10,900,000, white blood cells, 7,850, hemoglobin, 160 per cent (Sahli), and polymorphonuclears, 83 per cent. The results of the Wassermann test and the blood culture were negative.

A roentgenogram of the heart showed some left ventricular enlargement with rounded contour, no enlargement of the left auricle, of the base of the heart or of the great vessels, except for some slight prominence of the right border of the ascending aorta, the right border of the heart measured 32 cm and the left border, 92 cm. Fluoroscopy of the chest showed normal respiratory movements and apparently normal cardiac pulsations. The posterior mediastinum was clear.

An electrocardiogram showed a marked right preponderance, the only abnormal condition.

The vital capacity ranged from 2,100 to 2,500 cc. The blood pressure was 90 systolic and 60 diastolic. The pulse rate varied between 90 and 100, and the temperature varied between 99 and 100 F, with occasional sharp rises to 101 or 102 F.

Course—The course in the hospital was practically uneventful. The patient was able to walk about the ward without dyspnea. Cyanosis varied little. After three weeks in the ward, she was transferred to the Barach oxygen chamber, with the atmospheric oxygen maintained at from 44 to 46 per cent, and kept there three days. No important change was noted in the clinical condition or the physical signs during this period. She was again transferred to the ward, and discharged at the end of another week.

Diagnosis—The patient was seen by Dr R. L. Levy, who believed the condition undoubtedly to be congenital heart disease, probably involving a pulmonic stenosis and septal defect and possibly including the complete "tetralogy of Fallot"—pulmonic stenosis, septal defect, right ventricular hypertrophy and dextro-position of the aorta.

Experimental Studies—EXPERIMENT "A" The experimental studies made were as follows. On the first two occasions, March 13 and 18, arterial blood was drawn from the brachial artery, transferred under oil to a tube containing dried neutral potassium oxalate and sodium fluoride, and analyzed for oxygen content and capacity, and on March 18 for carbon dioxide content also. Analyses were made with the Van Slyke-Neill⁶ apparatus. On March 28, a complete experiment was done. With the patient under basal conditions, expired air was collected in a Douglas bag. After this, two sets of alveolar air and oxygenated mixed venous samples were obtained, the patient resting for about fifteen minutes between each set. Details of this procedure were published previously.⁷ After a further rest of about fifteen minutes, arterial blood was drawn from the brachial artery. Enough arterial blood was obtained to permit determinations to be made of the oxygen content and capacity, the carbon dioxide content and to plot one point on the carbon dioxide curve of oxygenated blood. An oxygenated carbon dioxide curve was drawn by using as a slope that of the oxygenated carbon dioxide curve of the case of congenital heart disease described by L. J. Henderson.⁸ As the patient in the latter case had both an oxygen capacity and a carbon dioxide capacity closely similar to those of our patient, such a procedure seemed justifiable. Displacements upward of points on the carbon dioxide diagram, due to oxygen unsaturation, were also estimated by the use of this same nomogram of Henderson's.

EXPERIMENT "B"—An experiment exactly similar to the foregoing one was done on April 1, after the patient had remained for three days in the oxygen chamber. On the day before, March 31, a respiration experiment was done, as described, but no blood drawn, the patient was not under basal conditions at this time, having finished breakfast about fifteen minutes before. From the work of Higgins⁹ and later that of Dodds,¹⁰ it was shown that at this interval after meals the alveolar carbon dioxide values are increased usually about 1 or 2 mm. A small effect of this sort is evident in our data, but this has no significant bearing on our general results.

The data obtained are given in the table

⁶ Van Slyke, D. D., and Neill, J. M. The Determination of Gases in the Blood by Manometric Measurement, *J. Biol. Chem.* **61** 523, 1924.

⁷ Richards, D. W., Jr., and Strauss, M. L. Circulatory Adjustment in Anemia, *J. Clin. Investigation* **5** 161, 1928.

⁸ Henderson, L. J. *Compt. rend. Acad. d. sc.* **18** 2066, 1925.

⁹ Higgins, H. L. Influence of Food, Posture, and Other Factors on the Alveolar Carbon Dioxide Tension in Man, *Am. J. Physiol.* **34** 114, 1914.

¹⁰ Dodds, E. C. Variations in Alveolar Carbon Dioxide Pressure in Relation to Meals, *J. Physiol.* **54** 342, 1921.

COMMENT

From the three initial experiments with arterial blood, it is clear that this patient had consistently an extraordinary degree of arterial oxygen unsaturation, as well as the usual marked polycythemia, the arterial saturation being on the three occasions 64, 55 and 60 per cent.

The pulmonary function, so far as the clinical examination showed, was normal or better than normal. There were no signs of congestion in the lungs. The patient's vital capacity, of from 2,000 to 2,500 cc, was large for a child of her size. The supplemental air measured from 700 to 1,000 cc, and the residual air approximated these figures. It was not likely that the lungs were greatly concerned in the production of arterial cyanosis.

This impression was proved beyond doubt when the patient was placed in the oxygen chamber, and the arterial oxygen saturation rose only 5 per cent, scarcely more than the change that would occur in a normal person. Thus, even in room air the pulmonary alveoli apparently oxygenated satisfactorily the blood that passed through them.

This patient was, therefore, one of those whose aorta and arterial systems contain a mixture of arterialized and venous blood.

Nature of the Mixing Process—The nature of the mixing process in the chambers of the heart can be more fully demonstrated in this case, with a fair degree of probability, by further examination of the data.

Consider the relation between the alveolar air and the arterial blood. If the samples of alveolar air are plotted on the carbon dioxide curve, it will be seen (the table and fig. 3) that the corresponding carbon dioxide content averaged about 29 per cent by volume, whereas the actual arterial carbon dioxide content is more than 9 per cent by volume higher. This is a large discrepancy and, of course, raises doubt at once as to the accuracy of the specimens of alveolar air, i. e., whether or not the samples of air obtained were actually in equilibrium with the blood in the pulmonary capillaries. In patients with cardiac disease the alveolar carbon dioxide is frequently low with respect to the arterial carbon dioxide tension, and although Meakins, Dautrebande and Fetter¹¹ showed that if (as here) arterial blood is used for the construction of the carbon dioxide curve this discrepancy disappears there are cases in which correspondence between alveolar and arterial tensions is not to be obtained even by the use of this technique. Such cases are usually complicated by advanced congestive heart failure and greatly lowered vital capacity.

11 Meakins, I. C., Dautrebande, L., and Fetter, W. J. The Blood Gases and Circulation Rate in Cases of Mitral Stenosis, *Heart* 10 153, 1923.

In the present instance there is every reason to believe that the alveolar samples were satisfactory. The patient had an excellent vital capacity, sufficient supplemental air and was cooperative and intelligent. The results were as consistent as one expects to get even with trained subjects. One possible further criticism should be considered. The

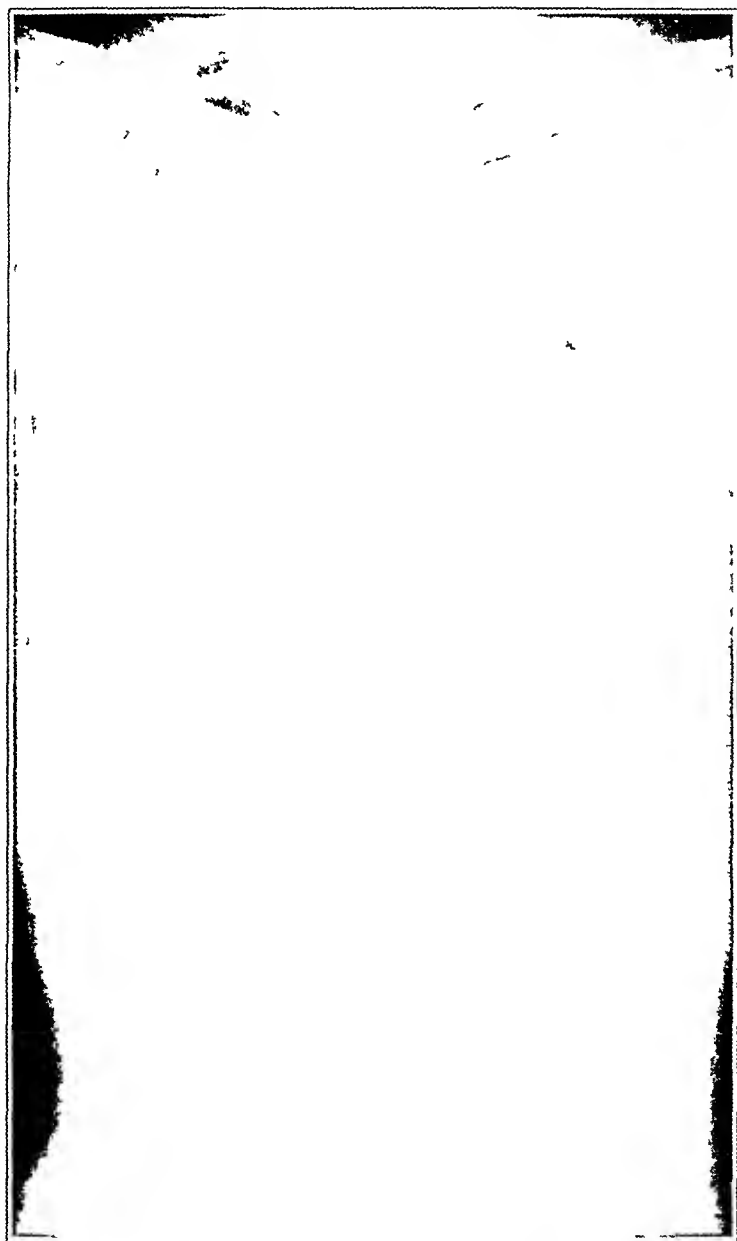


Fig 1—Roentgenogram of the heart taken from a distance of 6 ft

high ventilation of this subject and the high respiratory quotient (0.96) suggests that during the collection of expired air there may have been considerable overbreathing ("Auspumpung"), and that the alveolar carbon dioxide was lowered on this account. This seems unlikely, because, though one set of alveolar samples was always taken immediately after the end of the period of the collection of expired air, the

second set was obtained after a fifteen minute rest period, during which the patient was breathing normally and without the attachment of mouthpiece or nose clip. The only inconsistently low sample of the series was taken at such a time and not at the end of the collection of expired air.

With the pulmonary carbon dioxide, then, 9 per cent by volume lower than the arterial carbon dioxide, we have not only further proof of venous admixture in the arterial blood, but also an indication of a large arteriovenous difference in the pulmonary circulation, and hence a small pulmonary blood flow (pulmonary stenosis).

The investigation can be carried further by means of the oxygenated "mixed venous" (or pulmonary artery) carbon dioxide tension. It is not an easy matter to obtain reliable measurements of this value, chiefly because of the brief time that is available for the establishment of lung-blood equilibrium, before recirculation of the blood occurs. It has been our practice to use a rebreathing bag containing 2,500 cc of a mixture of carbon dioxide and oxygen, with an amount of carbon dioxide sufficient so that when it is mixed with the residual air in the lungs the resultant carbon dioxide will be about that of the (estimated) oxygenated venous carbon dioxide tension. The rebreathing from the bag is begun after a complete expiration has been made, and four complete respirations made in the next twenty (sometimes twenty-five) seconds. Samples are taken into evacuated tubes at the end of the third and fourth (on one occasion also at the end of the second) expiration, and a sample taken later from the bag after rebreathing is finished. This technic was followed in the present instance, furthermore, the initial carbon dioxide in the bag was varied widely. The results are plotted in figure 2, the initial bag carbon dioxide tension on the left, and the tensions after rebreathing for ten, fifteen, twenty or twenty-five seconds on the corresponding ordinates. It will be seen that, except in one experiment (the same as that in which a low alveolar air was obtained), the tensions at the end of fifteen and twenty seconds are grouped fairly well around 39 mm carbon dioxide tension, and this in spite of a variation of nearly 20 mm in the initial bag tensions. It seems fair to conclude that this represents an equilibrium value, and that 39 mm carbon dioxide tension (actual average 38.3 mm) is not far from the oxygenated pulmonary artery carbon dioxide level.

The interesting point about this is that when plotted on the oxygenated carbon dioxide curve (fig 3), 38.3 mm of carbon dioxide tension shows a value of 38.6 per cent by volume of carbon dioxide or close to the two values, (38.6 and 40.4 per cent by volume) for arterial carbon dioxide that were obtained by these two experiments. In other words, the blood in the pulmonary artery and the blood in the systemic aorta have essentially the same carbon dioxide content. The conclu-

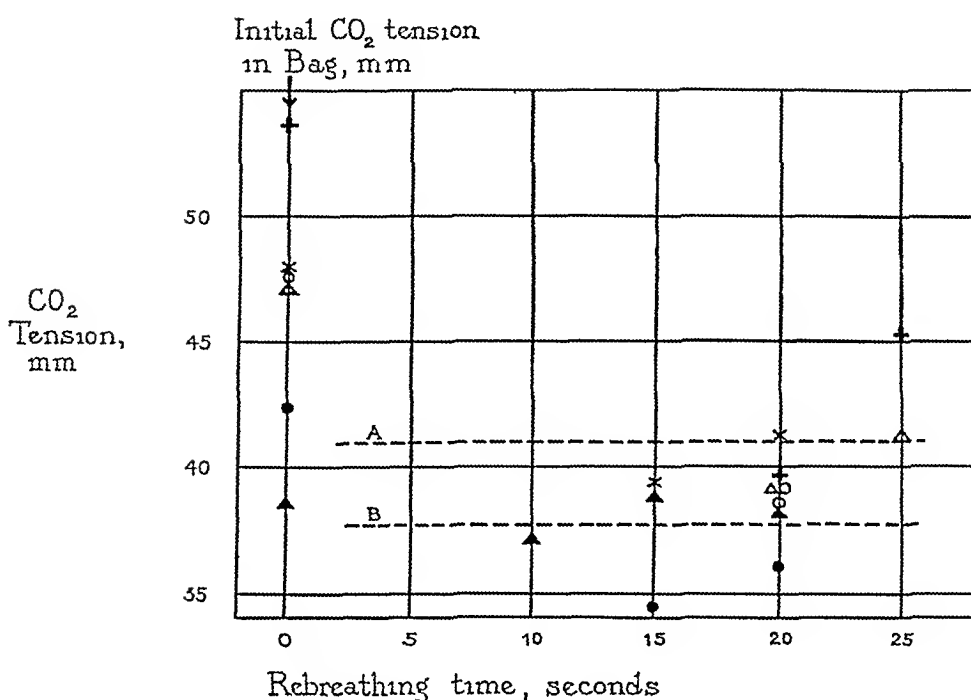


Fig 2—Oxygenated mixed venous tensions The circles equal the experiments made on March 28, in ordinary room air The crosses, plus marks and triangles equal the experiments made on March 31 and April 1, in the oxygen chamber The horizontal line, *A*, equals the carbon dioxide tension which the arterial blood on March 28 would have had if this blood had been completely oxygenated, without change in carbon dioxide content The line *B* equals the carbon dioxide tension, similarly, for oxygenated arterial blood on April 1

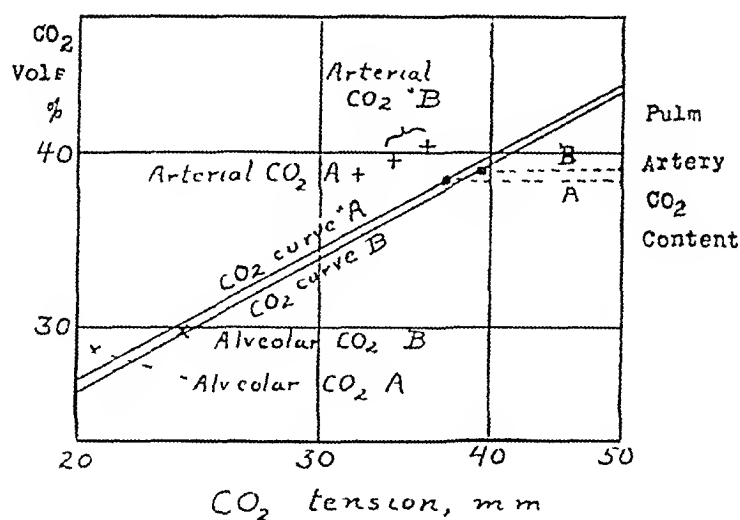


Fig 3—Chart showing the carbon dioxide dissociation curves of oxygenated blood, plotted logarithmically, experiment "A" done on March 28, with the patient in the ward, breathing room air, experiment "B" done on April 1, with the patient in the oxygen chamber, breathing an atmosphere of 45 per cent oxygen

sion to be drawn from this is obvious. That with which we apparently are dealing physiologically is an extensive septal defect, so that the blood coming in from the venae cavae and that from the pulmonary veins are mixed, and the blood going into the pulmonary artery during systole is the same as that going into the systemic aorta. Whether the septal defect is auricular or ventricular is unimportant from the present point of view.

It should be emphasized at this point that we do not consider our data exact, and cannot, therefore, insist that the mixture of the blood from the right auricle with that from the left auricle is actually complete. It is believed, however, that the general mechanism of the circulation in this case conforms to the description given, rather than that there is simply a bodily transfer of a certain volume of venous blood over to the left side of the heart, with no reciprocal mixture of the blood from the left with that from the right side of the heart.

There is one criticism against the oxygenated mixed venous values which comes to mind at once in a consideration of a three-chambered type of heart. The recirculation of blood would be expected to occur quickly and thus vitiate any attempt at mixed venous equilibrium. However, any error of this sort would cause the mixed venous values of carbon dioxide, as obtained, to be too high rather than too low, whereas the equilibrium values that we obtained were low, as low in fact as they could possibly be, without assuming some mechanism whereby more aerated blood could get back into the pulmonary artery than could get into the aorta.

It seems probable that the slow rate of pulmonary circulation with perhaps an increased volume of circulating pulmonary blood, delayed matters enough so that no great recirculation of blood occurred within twenty seconds.

It is evident, therefore, that with the data obtained the circulation in this case can be explained on the basis of a three-chambered type of heart. It is important to consider next whether the data are also consistent with another type of circulation assumed to exist in certain forms of congenitally malformed hearts, namely, a simple right-to-left shunting of a part of the systemic venous blood, e. g., from the right ventricle into the left. If the latter situation existed, the blood in the pulmonary artery would be a mixture of venous systemic blood. Furthermore, in such a case, irrespective of the amount of the shunt, the arteriovenous difference in the gases of the blood in the systemic circulation would be the difference between the pulmonary arterial content (of carbon dioxide or oxygen) and the systemic arterial content (of carbon dioxide or oxygen). If the carbon dioxide or oxygen content of pulmonary arterial blood approached more and more nearly to that of the systemic arteries, the arteriovenous difference would decrease, and the blood flow in the systemic circulation would be

increased correspondingly. When the two were the same, the blood flow (on the right-to-left shunt hypothesis) would become infinitely large.

In the present case, therefore, it is not possible to explain the data on the basis of a simple right-to-left shunting of venous blood. A simple left-to-right shunting is of course practically ruled out by the marked oxygen unsaturation of arterial blood, persisting in high oxygen atmospheres.

The flow of pulmonary blood, calculated from arteriovenous differences and carbon dioxide output, is given in the table. It will be seen

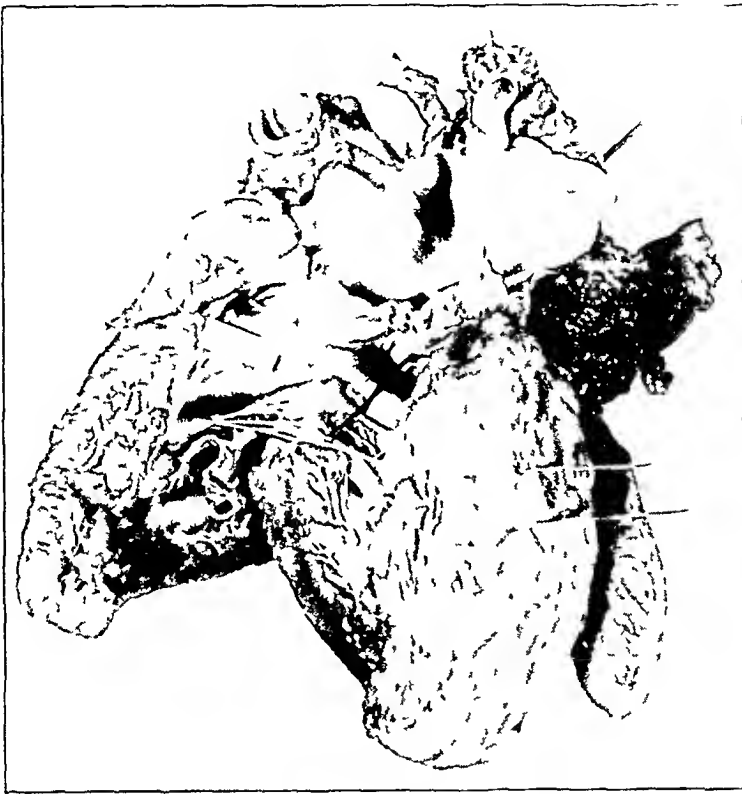


Fig 4—Heart of patient, A S, exposing the right ventricle and aorta. The right ventricular hypertrophy is well shown, as well as the origin of the aorta from the right ventricle. A probe passes from the right ventricle through the stenosed pulmonary artery orifice. Immediately below this orifice is the inter-ventricular septal defect.

that the volume flow both under conditions of the ward and of the oxygen chamber was about 2 liters a minute. This, of course, is a rather low value and suggests a certain amount of pulmonary stenosis.

With the pulmonary carbon dioxide, then, 9 per cent by volume quotient it is possible to make a few other tentative calculations. Our chief difficulty is in the respiratory quotient value. In the experiments made on March 28, the value 0.96 was obtained, this is almost

certainly too high, probably as a result of overbreathing. Using it for the calculation of the differences of arteriovenous oxygen, an average of 10 per cent by volume is found, and this added to the arterial oxygen gives 30.2 per cent by volume, or $\frac{30.2}{33.8} = 89.4$ per cent oxygen saturation of pulmonary vein blood. A respiratory quotient of 0.81 gives $\frac{32.1}{33.8} = 95$ per cent saturation, and this is probably nearer the truth. In the experiments made on March 31 and April 1, we were dealing with high oxygen atmospheres, and direct Haldane analyses were impossible, our actual analyses of the samples for oxygen were unfortunately not accurate, and no satisfactory respiratory quotient was obtained. If again an average respiratory quotient of 0.81 is assumed, the arteriovenous oxygen difference is 11 per cent by volume, and the pulmonary vein blood $\frac{32.5}{33.2} = 98$ per cent saturated, as one would expect.

So far as the blood flow through the systemic circulation is concerned, it is, of course, impossible to calculate a definite value. Henderson¹² found that the minimum tension of venous oxygen compatible with tissue metabolism is around from 20 to 25 mm. Taking the latter figure and using the nomogram of the congenital heart blood previously mentioned, one finds that this corresponds to an oxygen content of 14 per cent by volume. This gives an arteriovenous difference of $20.2 - 14 = 5.8$ per cent by volume, and a blood flow of $\frac{1.88}{5.8 \times 10} = 3.2$ liters per minute. This suggests that the systemic blood flow in this case is probably not less than about 3 liters a minute.

Other subsidiary points in our data that may be noted are (1) the practical absence of change in the values for blood gases as a result of putting the patient in the oxygen chamber, except for the 5 per cent rise in arterial oxygen saturation and (2) the patient's large pulmonary ventilation, not reduced by high atmospheric oxygen. As a matter of fact, the pulmonary ventilation increased slightly, but this was probably due to the fact that the oxygen chamber was not completely free from carbon dioxide, containing about 0.5 per cent of this gas. The high pulmonary ventilation, together with the large vital capacity, apparently represents real pulmonary hypertrophy and is a compensatory mechanism, making possible the large arteriovenous differences that are maintained between pulmonary arterial and pulmonary venous blood and the maintenance also of an alveolar air carbon dioxide value much below the arterial level.

The various types of intracardiac circulation that occur with different congenital malformations of the heart have been described in detail in monographs by Abbott.⁴ Many of these malformations

¹² Henderson, L. J. Blood, New Haven, Conn., Yale University Press, 1928.

involve a reciprocal mixing of venous and arterialized blood proximal to the point where the great vessels separate (a) septal defects, auricular, ventricular or aortic, (b) various transpositions of the great vessels, and (c) atresia of various orifices combined with patent ductus arteriosus, etc. From the study of the blood gases that we have just reported, it is not possible, therefore, to make an accurate diagnosis in the present case. Taking into consideration also the clinical, roentgen and electrocardiographic observations, we thought it probable that the case was either one of the tetralogy of Fallot,¹³ with rather extensive septal defect, or a cor biatritum trilobulare.

It may be noted in cases of this sort, with mixing of venous and arterial blood in a common chamber proximal to the great arterial vessels, that unless the mixing is fairly complete, it will be difficult to demonstrate it by blood gas measurements. If, for example, twice as much venous (vena cava) blood as pulmonary vein blood should go into the pulmonary artery, and also twice as much pulmonary vein blood as venous blood should pass into the systemic aorta, then the measured effects would be a higher systemic arterial content of carbon dioxide (due to mixture with venous blood) and a lower oxygen content, whereas the pulmonary artery blood would show a lower content of carbon dioxide (due to mixture with pulmonary vein blood) and a higher oxygen content. It might not be possible to say from the data, however, whether this state of affairs was due to the given amount of reciprocal mixing or to a simple right-to-left shunt, combined with a more rapid systemic circulation rate (and so more "arterialized" vena cava blood). It is only when pulmonary artery and arterial blood carbon dioxide contents approach equality that it becomes impossible to explain the picture on any basis other than reciprocal mixing, when pulmonary artery and systemic arterial blood gases differ by small amounts, a certain amount of reciprocal mixing becomes highly probable, but the exact relation between such mixing and the rate of the systemic circulation cannot be calculated.

The foregoing argument was written on the basis of clinical and experimental data, while the patient was still living.

Second Admission—The patient was readmitted to the hospital on May 7, 1930, with a history of headache and vomiting for ten days, and paralysis of the left leg for four days. During the next five days the paralysis extended over the whole left side. She became increasingly weak and stuporous, and died on May 12, 1930. It was noteworthy that there were no pronounced symptoms of cardiac failure, the pulse remaining steady and respiration slow and regular almost to the end. Death was thought to be due to progressive thrombosis in the cerebral blood vessels.

13 Fallot, A. Contribution à l'anatomie de la maladie bleue, *Marseilles med* 25 77, 138, 207, 270, 371 and 403, 1888.

Autopsy—Autopsy was performed on May 12

Heart The length of the heart from the superior margin of the right auricular appendage to the apex measured 11 cm. The base at the level of the aortic outlet measured 7 cm and the anteroposterior diameter, 7.5 cm. The heart was globular and the apex was wide and blunt. The foramen ovale was closed. The leaflets of the tricuspid valve were thin and delicate. On the line of the closure of the infundibular leaflet was one small, yellowish-gray, pyramidal nodule measuring less than 1 mm in width. The chordae tendineae were slender. The endocardium of the right ventricle was thickened over its entire surface. The papillary muscles and columnae carnae were large, and the ventricular wall was markedly hypertrophied, measuring 1.5 cm in thickness. The aorta took its origin from the right ventricle. Three leaflets were present in the aortic valve, and these were equal in size. The posterior cusps were joined by a wedge-shaped mass which measured 7 mm in width at the margin of the valve. This was 5 mm in thickness and extended backward, joining the segments of the valve, to the point of junction with the aorta. Beneath the endocardium this mass appeared to be reddish gray. The margins of the posterior valve leaflets adherent to the mass were thickened and somewhat rolled, a process which extended across part of each leaflet. The margin of the anterior leaflet, at its center, was also somewhat thickened and slightly nodular. In the interventricular septum, situated just below the level of the aortic valve leaflets, was an opening 1.5 cm in its greatest diameter. The lower margin of this was formed by the muscular wall of the septum, while the upper margin was formed by the left posterior leaflet of the aortic valve and the pulmonic valve. The pulmonic valve appeared as a thick membrane in which there was a longitudinal opening about 7 mm in length but only from 2 to 3 mm in width. On the ventricular surface two small triangular elevations extended outward from each end of the slitlike orifice to the pulmonic ring, thus giving the appearance of two large and two small fused sectors. The pulmonic valve overrode the septal defect, lying slightly more to the left than to the right, the pulmonary orifice thus opening from the left ventricle. The endocardium of the left auricle was of normal thickness, that of the left ventricle was slightly thickened throughout. The leaflets of the mitral valve were not thickened, and the chordae tendineae were slender. The papillary muscles rose in three adjoining columns from the lateral wall of the left ventricle, and were not hypertrophied. The myocardium of the left ventricle measured 12 mm in thickness. The muscles of both right and left ventricles were deep brownish red and firm.

The measurements of the heart were: tricuspid valve, 7 cm, orifice of the pulmonic valve, 7 by from 2 to 3 mm, aortic valve, 6 cm, mitral valve, 6 cm, right ventricle, 1.5 cm and left ventricle, 12 cm.

The coronary arteries rose below the level of the highest points of attachment of the aortic valve leaflets, from the sinuses behind the posterior segments of the valve. The right artery sent a branch to the left ventricle, supplying its posterior half. The left artery divided into the two usual branches, the anterior descending branch and the circumflex.

Aorta The ascending aorta measured 6.5 cm in circumference in its ascending portion. At the level of the patent ductus it measured 4.2 cm in circumference and at the level of the superior mesenteric artery, 3.2 cm. The intimal surface was pale yellow. The aorta was elastic. The ductus arteriosus was open, its orifice measuring 8 by 5 mm in size.

Pulmonary Artery and Ductus Arteriosus The pulmonary artery lay to the left and, in part, posterior to the aorta, and measured 1.5 cm in diameter. Five millimeters above its bifurcation, the patent ductus arteriosus entered the left

pulmonary artery, its lumen being about 2 mm in diameter at this point. The ductus measured 1.5 cm in length.

The bronchial arteries seemed large for the age of the patient, that to the left bronchus measuring 3 mm in diameter, while that to the right measured about 2.5 mm.

Anatomic Diagnosis—The anatomic diagnosis was congenital pulmonary stenosis, a defect of the interventricular septum, transposition of the great arterial trunks, hypertrophy of the right ventricle, patent ductus arteriosus, congestion of the viscera, abscess of the brain with rupture into the right lateral ventricle and localized acute leptomeningitis.

COMMENT

Clinical versus Pathologic Observations—A comparison of the clinical with the pathologic observations is interesting. That the blood in the pulmonary arterial system and the blood in the systemic arterial system were essentially the same in respect to the content of gases is definitely confirmed, for, with the extreme dextroposition of the aorta even further to the right than the pulmonary artery, the former vessel could hardly have received more highly aerated blood than the latter. The venous blood from the right auricle evidently mixed with that from the left ventricle, the latter coming in through the large septal defect. The mixed blood then passed out largely through the aorta, although a small part passed through the stenosed pulmonary artery. The pulmonary circulation was increased by the passage of some aortic blood through the patent ductus arteriosus, and perhaps also through the enlarged bronchial arteries.

From the physiologic standpoint, therefore, the circulation was that of a three-chambered heart.

A further possibility should be mentioned, namely, that the pulmonary artery actually received blood that was better aerated than did the aorta, due to the position of the pulmonary orifice immediately above the septal defect. The fact that the pulmonary artery carbon dioxide (see the table) was measurably less than the systemic arterial carbon dioxide points in the same direction, but the technic was not accurate enough to make this evidence definite.

The exact pathology of the heart was obviously not deduced from the clinical studies, the diagnosis of patent ductus arteriosus was not made. It might have been suspected from the double murmur at the base of the heart combined with the accentuated pulmonic second sound.

As to the extent of pulmonary stenosis, the experimental data seemed to show that the pulmonary blood flow was roughly half the systemic, 2, as compared with about 3.5 liters per minute. The small size at autopsy of the opening of the pulmonary artery and of the ductus arteriosus at its pulmonary end suggests that the pulmonary blood flow was even less than 2 liters. It is not possible to adduce definite figures on this point—measurements of the size of the orifices of these vessels

at autopsy would not necessarily be proportional to their sizes during life, and pressure relations would be difficult to estimate

The extensive hypertrophy of the lungs in this case is clearly explained, as suggested, by the small pulmonary blood flow

From the point of view of experimental method, this study has been of especial interest in that the technic employed is shown to have given fairly accurate results with at least one type of pathologic circulation. It is not often that a technic for measuring the blood flow can be satisfactorily verified in man

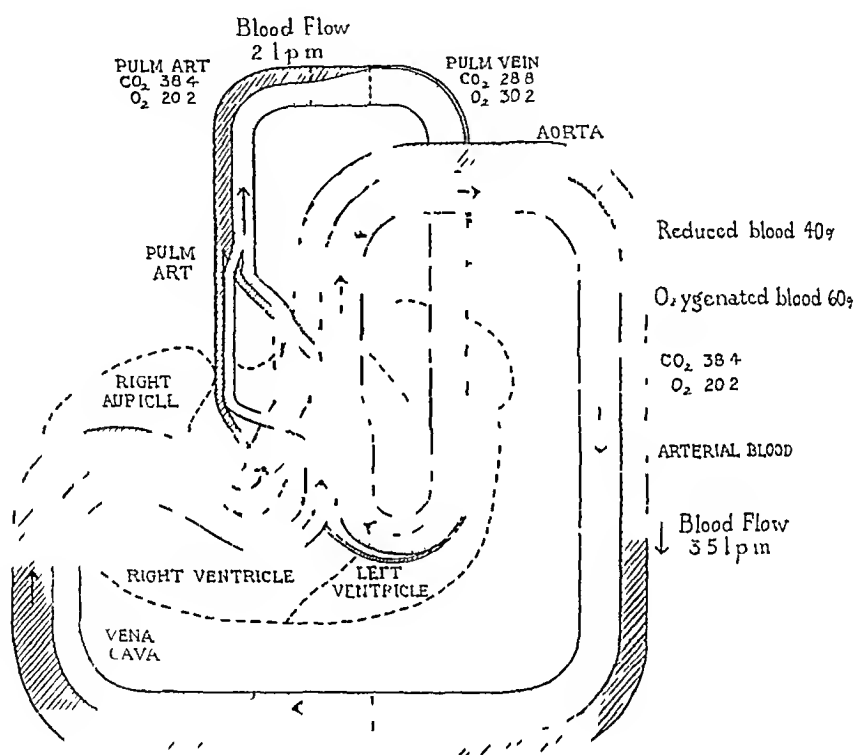


Fig 5—Diagrammatic representation of the circulation (tetralogy of Fallot, combined with patent ductus arteriosus). The blood flow, in liters per minute, is represented by the width of blood vessels in the diagram. The hatched areas represent the reduced blood and the dotted areas, the oxygenated blood. For purposes of illustration, reduced and oxygenated blood are represented as flowing separately in blood vessels. D-A is the ductus arteriosus. The figures for carbon dioxide and oxygen are taken from the experiment performed on March 28, except that the pulmonary artery carbon dioxide (38.3) and the arterial carbon dioxide (38.6) are both taken as 38.4 on the assumption that the blood in these two vessels is identical.

A diagram of the circulation in this case is given in figure 5. In it an attempt has been made to show both the course of the circulation and the approximate amounts flowing in each part. The systemic circulation, based on the assumption noted in previous paragraphs, is

taken as 3.5 liters per minute. For purposes of illustration, the pulmonary artery and ductus arteriosus are assumed to contribute equal amounts to the pulmonary circulation.

SUMMARY

Clinical, physiologic and pathologic studies have been made in a case of congenital malformation of the heart, the anatomic lesions of which were those forming the tetralogy of Fallot combined with a patent ductus arteriosus.

The course of the circulation is described.

Dr. A. L. Barach cooperated with us in the use of the oxygen chamber, and Dr. Beryl Paige prepared and described the pathologic material.

HYPERTENSION IN CASES OF CONGENITAL POLYCYSTIC KIDNEY*

FREDERICK W SCHACHT, M D

WINNETKA, ILL

The presence of persistent hypertension in cases of congenital polycystic kidney has been a disputed point in the literature. Various investigators¹ have called attention to the high incidence of hypertension associated with this condition. In 1928, Bell and Clawson,² after a review of the literature and a study of eight cases, concluded "The available information is strongly against the view that congenital cystic disease of the kidneys is accompanied by persistent hypertension."

In 1914, Veil³ studied three cases in which a definite diagnosis of polycystic kidney had been made at a clinical examination. The patients were women, aged between 42 and 50. In each case the heart was not enlarged, but the blood pressure was elevated. Veil maintained that the absence of cardiac hypertrophy was against persistent hypertension, and because there was not marked renal insufficiency, he did not think that the hypertension could be of renal origin.

In a review of 193 cases of polycystic kidney at the Mayo Clinic, one of the most striking abnormalities noted was the number of patients with hyperpiesis. In this group, the systolic pressure in 61 per cent was 145 mm of mercury, or more, whereas in 55 per cent the diastolic pressure was 90 mm of mercury, or more. This observation led me to make more intensive investigations.

For the present investigation, I chose the records of patients with a polycystic kidney, who had died. These records furnished seventy-four

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1 Braasch, W F. Clinical Data of Polycystic Kidney, Surg Gynec Obst **23** 697 (Dec) 1916. Ritter, S A, and Baehr, George. The Arterial Supply of the Congenital Polycystic Kidney and Its Relation to the Clinical Picture, J Urol **21** 583 (May) 1929. Vollard, Franz, and Fahr, Karl. Die Brightsche Nierenkrankheit, Berlin, Julius Springer, 1914.

2 Bell, E T, and Clawson, B J. Primary (Essential) Hypertension. A Study of Four Hundred and Twenty Cases, Arch Path **5** 939 (June) 1928.

3 Veil, quoted by Rosenberg, Max, and Munter, Friedrich. Zur Frage der renalen oder extrarenalen Blutdrucksteigerung, Deutsche med Wchnschr **50** 1437 (Oct) 1924.

cases, in which the blood pressure was noted at least once in seventy-two cases, and frequently it was noted several times. The incidence of hypertension in this group was 75 per cent, the systolic level of 145 mm of mercury had been chosen as indicating elevated blood pressure. In order to eliminate the factors of age, sex and renal infection, a group of seventy-two patients of corresponding age and sex, with chronic bilateral pyelonephritis, was studied with reference to the blood pressure, the size of the heart and the changes in the eyegrounds. In this group, the blood pressure was elevated in only 26 per cent.

REVIEW OF THE LITERATURE

In 1850, Johnson,⁴ in describing the arteries of the kidney in chronic interstitial nephritis, stated "In the healthy vessel the inner coat is thinner than the outer, but in a diseased condition I have generally found them of nearly equal thickness. The two coats appear to be the same nature and in all probability they are muscular. The thickening appears to be proportionally greater in the smallest arteries." In 1868, he reported⁵ the results of further experiments that confirmed his first observation, and he continued, "In every fatal case of chronic Bright's disease with hypertrophy of the left ventricle, there has been decided hypertrophy of the arterial walls in most of the tissues examined, not only in the kidneys, but also in the skin, the intestines, the muscles and the pia mater."

In 1872, Gull and Sutton⁶ maintained "The marked change in the arteries and capillaries is the primary and essential condition of the morbid state called chronic Bright's disease with contracted kidney." Various arterioles and small arteries, situated chiefly in the pia mater, kidney, skin, stomach, spleen, lung, heart and retina, were measured by these investigators.

In 1877, Ewald⁷ studied sixty-two cases of contracted kidney, and found muscular thickening of the arterioles and hypertrophy of the muscles of the heart in almost all cases of chronic granular interstitial nephritis.

4 Johnson, George. On the Proximate Cause of Albuminous Urine and Dropsy, and on the Pathology of the Renal Blood Vessels in Bright's Disease, *Tr Med-Chir Soc London* **33** 107, 1850.

5 Johnson, George. I On Certain Points in the Anatomy and Pathology of Bright's Disease of the Kidney, II On the Influence of the Minute Blood Vessels upon the Circulation, *Tr Med-Chir Soc London* **51** 57, 1868.

6 Gull, W. W., and Sutton, H. G. On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease with Contracted Kidney, *Tr Med-Chir Soc London* **55** 273, 1872.

7 Ewald, C. A. Ueber die Veränderungen kleiner Gefässe bei Morbus Brightii und die darauf bezüglichen Theorien, *Virchows Arch f path Anat* **71** 453 (Dec) 1877.

In 1904, Jores⁸ found vascular alteration in which the intima had undergone fatty and hyaline degeneration and the internal elastic membrane was markedly thickened. However, in a single case, he noted definite thickening of the muscle of the media of the arterioles in many organs, including the arterioles of the skeletal muscle. In this case there was also a disturbed ratio between the thickness of the wall of the vessel and the lumen of the arterioles.

In 1916, Fahr⁹ called attention to a "necrotic process of the walls of the small arteries and arterioles, with destruction of the renal parenchyma", because of its serious nature, he termed the condition malignant renal sclerosis.

In 1928, Keith, Wagener and Kernohan¹⁰ showed narrowing of the arterioles and small arteries in many organs, including the voluntary muscles, in a group of cases of hypertension in which the course was rapidly fatal. They termed the condition malignant hypertension. They noted a characteristic retinal picture, the age incidence, the absence of anemia and the frequent adequacy of renal function. In 1929, these investigators¹¹ concluded, "The arterioles in voluntary muscle of ambulatory patients with diffuse hypertensive disease frequently show distinctive histologic changes. These changes differ in degree and may afford a valuable index for predicting the ultimate outcome of the individual case."

A study of the arteries of the polycystic kidney by the method of injection was carried out by Hinman and Morrison¹² and Ritter and Baehr¹³. They demonstrated marked reduction in the caliber of the arteries in the polycystic kidneys that were injected.

The most popularly accepted limit of normal systolic blood pressure for the adult lies in a range of from 140 to 150 mm of mercury. Bell considered a persistent systolic pressure of 150 mm as the highest limit of normal in adults of middle age. Alvarez¹⁴ found a systolic pressure

8 Jores, L. Ueber die Arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis, *Virchows Arch f path Anat* **178** 367 (Dec) 1904

9 Fahr, T. Ueber maligne Nierensklerose (Kombinationsform), *Centralbl f allg Path u path Anat* **27** 481 (Nov) 1916

10 Keith, N. M., Wagener, H. P., and Kernohan, J. W. The Syndrome of Malignant Hypertension, *Arch Int Med* **41** 141 (Feb) 1928

11 Kernohan, J. W., Anderson, E. W., and Keith, N. M. The Arterioles in Cases of Hypertension, *Arch Int Med* **44** 395 (Sept) 1929

12 Hinman, F., and Morrison, D. M. Comparative Study of Circulatory Changes in Hydronephrosis, Caseo-Cavernous Tuberculosis and Polycystic Kidney, *J Urol* **11** 131 (Feb) 1924

13 Ritter and Baehr (footnote 1, second reference)

14 Alvarez, W. C. Blood Pressure in University Freshmen and Office Patients, *Arch Int Med* **26** 381 (Oct) 1920

of 140 mm in men and of 130 mm in women Janeway¹⁵ was of the opinion that any pressure of 135 mm up to middle life, and 145 or 150 mm thereafter, was abnormal The presence of persistent or significant hypertension can usually be established either by frequent periodic readings of the blood pressure or by examination of the fundus of the eye Fisher¹⁶ found that the average systolic blood pressure in a large group of persons was from 116 mm at the age of 16 to 136 mm at the age of 65

Comparison of Measurements of Renal Vessels

Observation	Cases of Polycystic Kidney			Control Group		
	Vessels Measured	Average Ratio of Wall to Lumen	Average Diameter of Vessels, Microns	Vessels Measured	Average Ratio of Wall to Lumen	Average Diameter of Vessels, Microns
1	11	1.098 ± 0.09	63	8	1.207 ± 0.12	68
2	9	1.118 ± 0.07	42	10	1.248 ± 0.15	55
3	10	1.148 ± 0.10	44	9	1.222 ± 0.10	48
4	10	1.136 ± 0.13	45	10	1.203 ± 0.13	36
5	10	1.096 ± 0.04	25	11	1.190 ± 0.09	29
6	6	1.137 ± 0.08	65	10	1.219 ± 0.16	36
7	10	1.129 ± 0.10	75	8	1.244 ± 0.04	50
8	10	1.155 ± 0.13	50	10	1.216 ± 0.09	28
9	10	1.131 ± 0.11	55	11	1.198 ± 0.17	29
10	10	1.143 ± 0.10	67	8	1.197 ± 0.11	35
11	10	1.126 ± 0.09	53	10	1.208 ± 0.15	50
12	10	1.115 ± 0.08	68	8	1.242 ± 0.14	30
13	10	1.123 ± 0.17	46	9	1.259 ± 0.19	42
14	7	1.144 ± 0.12	30	10	1.246 ± 0.12	50
15	8	1.185 ± 0.19	50	10	1.238 ± 0.12	42
16	10	1.119 ± 0.09	50	8	1.217 ± 0.15	47
17	9	1.144 ± 0.11	46	10	1.207 ± 0.10	40
18	10	1.117 ± 0.05	35	10	1.216 ± 0.09	35
19	10	1.121 ± 0.09	50	9	1.211 ± 0.11	50

CLINICAL DATA

The clinical data taken from the records of seventy-four patients who had died are shown in the accompanying table, a diagnosis of polycystic kidney was made in all of these cases In this group, composed of twenty-five women and forty-nine men, the average age at the time of death was 50 The blood pressure was noted in seventy-two cases The systolic blood pressure was found to be 145 mm of mercury or more in fifty-four cases (75 per cent) The diastolic pressure was

¹⁵ Janeway, T. C. Important Contributions to Clinical Medicine During the Past Thirty Years from the Study of Human Blood Pressure, *Bull. Johns Hopkins Hosp.* **26** 341 (Oct.) 1915

¹⁶ Fisher, J. W., quoted by Norris, G. W., Bazett, H. C., and McMillan, T. M. Blood-Pressure, Its Clinical Applications, Philadelphia: Lea & Febiger, 1927

more than 95 mm of mercury in forty-two cases (58 per cent). Examination of the retina revealed sclerosis of the retinal arterioles in 68 per cent

Wagener¹⁷ recently stated "In my opinion all of the branches of the central artery usually studied with the ophthalmoscope are arterioles. Visible sclerosis of these vessels, not secondary to primary disease of the optic nerve, of the retina or of the choroid coat, is practically always evidence of hypertensive disease, whether or not the readings of blood pressure are high at the time of examination The same processes observed in the retina are going on in the arterioles throughout the body "

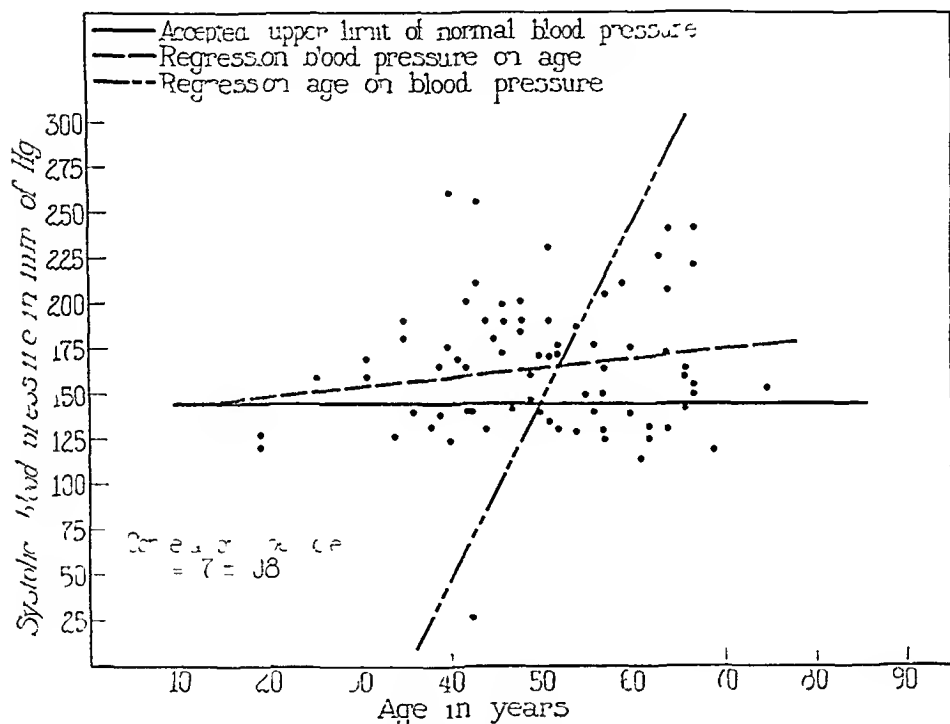


Fig 1—Polycystic kidney with systolic blood pressure plotted according to the age The large number of cases in which the blood pressure was above 145 mm of mercury and the lack of correlation between age and blood pressure may be noted

Cardiac enlargement was evident in 32 per cent of the cases observed by me Hypertension occurred in twenty-eight cases in which the age did not exceed 52 and in twenty-six cases in which it was more than 52 The coefficient of correlation between the age and the blood pressure was found to be 0.17 ± 0.08 (fig 1) In other words, in the majority of these cases the element of age was not the main factor causing the hypertension, as there was almost no correlation between the age and the blood pressure in this group of patients with polycystic disease of the

17 Wagener, H P Retinal Vascular Changes in Hypertension, Proc Staff Meet, Mayo Clin 5 203 (July 23) 1930

kidneys. If this hypertension resulted because of the general wear and tear on the cardiovascular system, a much closer correlation between the readings for the age and the blood pressure would be disclosed.

In 86 per cent of the cases in this group, definite evidence of renal insufficiency was shown by determinations of the urea or the phenol-sulphonphthalein. Anemia was revealed in 66 per cent. The specific gravity was below 1.010 in most of the cases. In approximately 70 per cent, albuminuria graded 2 was shown.

CONTROLS

A study of seventy-two cases of pyelonephritis (in subjects of corresponding sex and age) was carried out. This group was chosen in order to eliminate as far as possible the influence of age, sex, renal infection and the like on the blood pressure. In 26 per cent of these

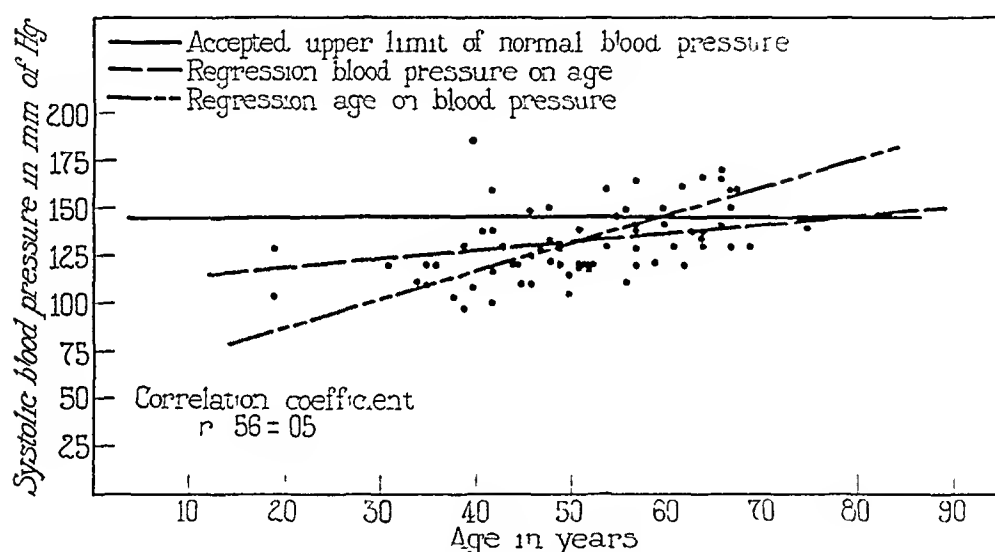


Fig 2—Patients with pyelonephritis of age and sex corresponding to cases in figure 1. The large number whose blood pressure was below 145 mm of mercury, and the close correlation (0.56) between age and blood pressure may be noted. This is similar to correlations between height and weight of human beings, as noted by Thurstone.

cases the readings of the blood pressure were indicative of hypertension. In 24 per cent, the retinal examination revealed sclerotic changes in the eyegrounds. Associated retinitis was not noted in this group. Cardiac enlargement was noted in 8 per cent.

Correlation between age and blood pressure was also found in this group. The coefficient was 0.56 ± 0.05 , which was comparable to the correlation found by Thurstone,¹⁸ between height in inches and weight in pounds in human beings (fig 2). The hypertension in this control

¹⁸ Thurstone L. L. Fundamentals of Statistics. New York: The Macmillan Company, 1925, p. 202.

group is dependent largely on the factor of age just as it would be in practically every other condition, although the general average reading of the blood pressure is slightly higher than normal because of the renal infection and its aftermath

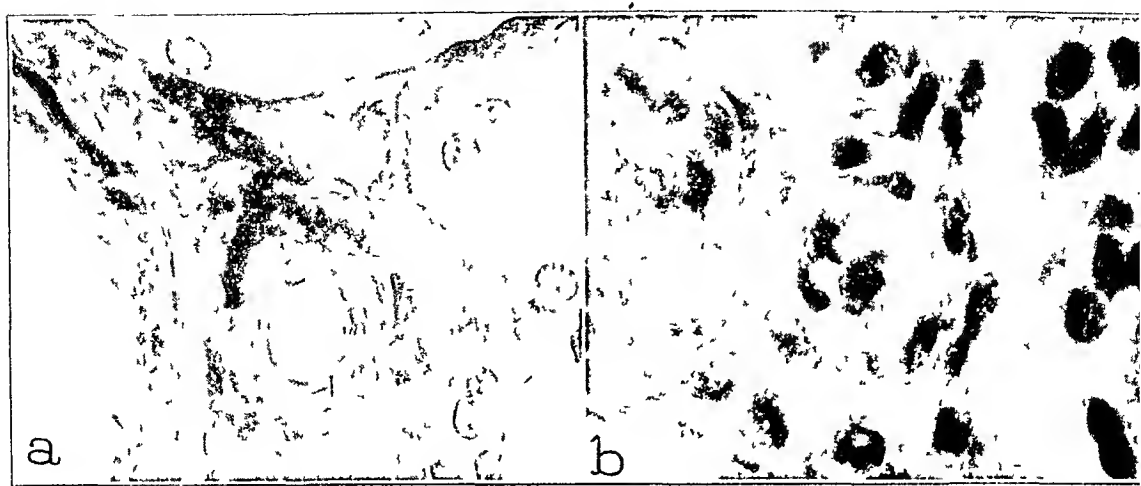


Fig 3—*a*, normal arteriole adjacent to the glomerular capsule. The relation of the wall to the lumen may be noted. Van Gieson's stain, $\times 650$. *b*, arteriole in a polycystic kidney with the lumen almost obliterated by nuclear proliferation adjacent to the glomerulus. Hematoxylin and eosin stain, $\times 750$.

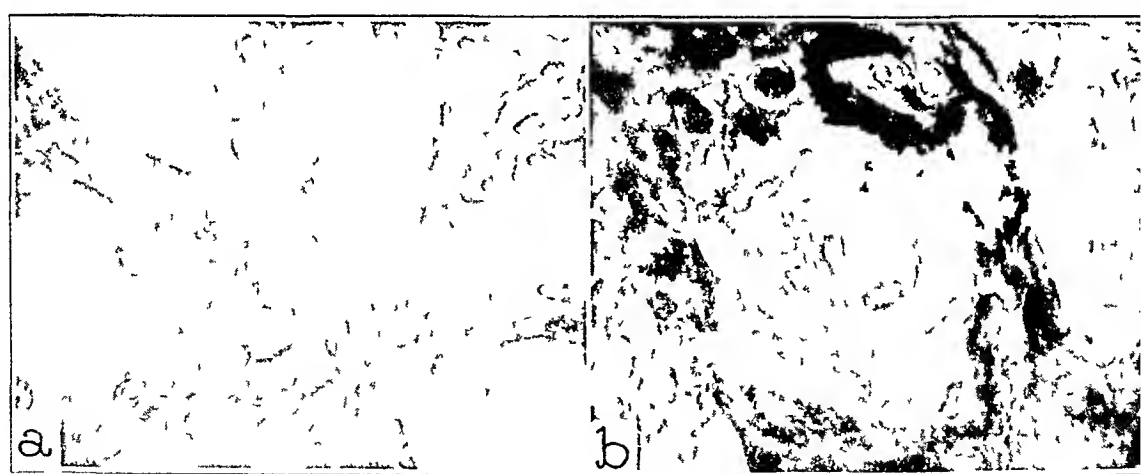


Fig 4—*a*, an afferent arteriole in an apparently normal kidney. Hematoxylin and eosin stain, $\times 650$. *b*, an arteriole in a polycystic kidney, marked thickening of the media may be noted. Van Gieson's stain, $\times 750$.

RENAL VESSELS

Nineteen polycystic kidneys were available for microscopic studies (figs 3*b* and 4*b*). Representative sections were made from several areas of each kidney and the tissues were stained with hematoxylin and eosin, Wiegert's elastic tissue stain and van Gieson's connective tissue stain.

As controls, nineteen kidneys were selected from patients of the same age and sex in whom death had occurred following a condition other than cardiovascular renal disease (figs 3a and 4a). The same stains and technic were employed. The measurements were made after the method of Keimohan with a Bausch and Lomb micrometer, care being taken to select the vessels cut at right angles.

The diameter of the small arteries and the arterioles was obtained in each case. From eight to twelve arterioles and small arteries were measured in each polycystic kidney and in each normal kidney, and the average size for each group was computed. The probable error for each

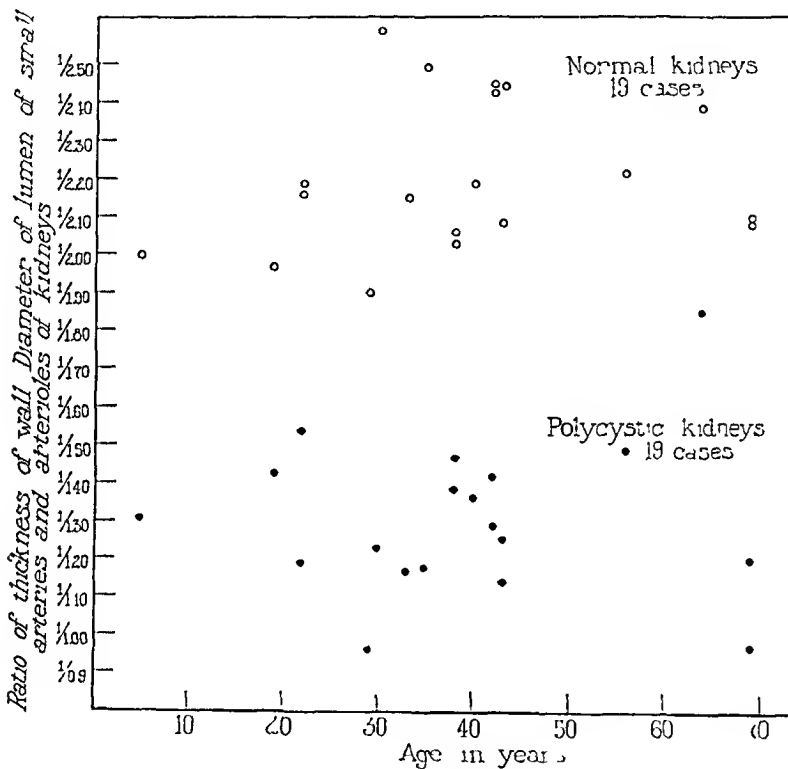


Fig 5—The average of individual readings of each case is shown charted as dots in cases of polycystic kidney, they are also arranged according to the age of the patient. The control groups are charted in a similar manner, in circles.

group of measurements was also calculated. Under these circumstances, the same factors of error tend to be carried from one group to the other, and any serious source of error is avoided.

Such measurements of the arterioles show that in the normal kidney the ratio of the wall to the lumen varies from 1.190 to 1.259, and the average ratio was approximately 1.220, as noted in figure 5.

The variation between the vessels that were measured in one subject was found to be approximately the same as the variation between the averages of different subjects (table).

The variations in the vessels of the polycystic kidney taken from subjects of the same age and sex as those in the control group averaged

from 1 096 to 1 185, with most of the cases occurring between a ratio of from 1 115 to 1 140. Thus a variation is seen within the group of polycystic kidneys as in the group of normal kidneys, but there is a wide and consistent difference between the two groups (fig 5)

COMMENT

The question of hypertension occurring with congenital polycystic disease of the kidney has been an interesting point in the literature. Hypertension has been explained on a purely renal basis by some authors.¹⁹ However, the presence of hypertension in congenital polycystic disease of the kidney is not necessarily secondary to renal changes. Since retinal sclerosis is present in a high percentage of cases, and since it is found more frequently than the secondary factor of cardiac enlargement, it seems probable that the sclerosis is more closely related to the cause than to the result of hypertension. Cardiac hypertrophy was found on clinical observation in 32 per cent of the cases in this series. There can be no doubt that if all of the hearts in this series had been available for weighing, many more would have been found larger than normal since it is extremely difficult to observe slight enlargement of the heart in a living person.

Peripheral sclerosis, a clinical observation, is rarely recorded with a high degree of accuracy, and unless observed by one specially interested in this subject, it is frequently not noted. This probably explains the discrepancy between the retinal and the peripheral sclerosis in this study. The importance of retinal sclerosis in any studies of hypertension cannot be overemphasized when properly controlled.

Renal vascular change undoubtedly is significant in the clinical picture of congenital polycystic kidney. The marked mechanical interference on the vascular pattern with consequent stretching and straining of the arteries and arterioles, the increase in the thickness in the walls of the arterioles and of the small arteries are facts which have not been previously emphasized in the study of this group of cases of renal insufficiency.

Furthermore, the proper study of any group of cases of hypertension should include a fairly selected control group which offers opportunity to compare and include such factors as age, sex, chronicity and peculiarities of the organs. It is thought that these requisites have been thoroughly considered in choosing a control group of cases of chronic pyelonephritis.

¹⁹ Fahr, T. Ueber die Beziehungen von Arteriolensklerose, Hypertonie und Hertzhypertrophie, *Virchows Arch f path Anat* **239** 41, 1922. Passler and Henike. Versuche zur Pathologie des Morbus Brightii, *Verhandl d deutsch path Gesellsch* **9** 99 (Sept) 1905.

SUMMARY AND CONCLUSIONS

1 Evidence at hand indicates that in the majority of cases of polycystic kidney, significant or persistent hypertension is present

2 There is marked thickening of the walls of the arterioles and of the small arteries of the polycystic kidney, with consequent reduction in the ratio between the thickness of the wall and the diameter of the lumen of the vessels of the kidney

3 The high incidence of retinal sclerosis in these cases indicates that the process probably is associated with a generalized vascular disturbance

228 Myrtle Street

Book Reviews

LE DIABLTE SUCRE SON TRAITEMENT By P A CARRIE Price, 20 francs
Pp 91 Paris Gaston Doin & Cie, 1930

It is a general fault of articles in the French literature that practically no attention is paid to the matter of bibliography Carrie's treatise is no exception, and this detracts considerably from the value of the book to those who may wish to go to original sources for confirmation of the statements made in the text Such neglect of the literature gives the impression that the authority of the professor's spoken word is supreme in France, and that the critical questioning of authority which has developed, particularly in Germany and America, and which is so stimulating to progress, is sadly lacking there

A few errors are noted The author, for instance, in a footnote implies that alcohol is converted into sugar He also contrasts the ketogenic-antiketogenic ratio, 2 1, of Shaffer with the 4 1 ratio of Ladd and Palmer, overlooking the fact that Shaffer's ratio is one of molecules of fatty acid to molecules of dextrose, whereas Ladd and Palmer expressed the proportions in terms of grams of fat to grams of carbohydrate When recalculated into molecules, Ladd and Palmer's ratio is essentially the same as that of Shaffer

It is also evident from the context that the author has not comprehended the fact that these ratios are significant only as far as they express the proportions of the various food factors actually metabolizing The ratio of the factors in the diet will be the same as that of foods metabolizing only when none of the food eaten is stored and all caloric requirements are perfectly satisfied

The treatment for coma, from the point of view of many American clinicians, is inadequate The use of alkali is reserved for cases in which insulin is temporarily unobtainable, and little or no attention is paid to the important question of providing fluids to combat dehydration

The reviewer is further dissatisfied with the consideration given the question of diabetes in pregnancy He has not observed increasing severity as pregnancy progresses, on the contrary, in many instances the tolerance increases in the later months of pregnancy and continues high during lactation Nor does he agree with the unqualified statement that nursing the infant aggravates the mother's diabetes

Despite these few objections, the reviewer finds himself in sympathy with the author's views The treatise is an excellent presentation of a method of treating patients with diabetes, which resembles closely that in use in the leading American clinics, a method in which empiricism has been replaced by a scientifically adjusted dietary and the precise use of the now available substitution therapy

TEXT-BOOK OF MEDICINE Edited by RUSSELL L CECIL, A B, M D, Sc D,
Assistant Professor of Clinical Medicine in Cornell University, Assistant
Visiting Physician in Bellevue Hospital, New York, and Associate Editor
for Diseases of the Nervous System, FOSTER KENNEDY, M D, F R S E,
Professor of Neurology in Cornell University, Head of Neurological Department,
Bellevue Hospital Second edition, revised and entirely reset—Cloth
Price, \$9 Pp 1,592 Philadelphia W B Saunders Company, 1930

The first edition of Cecil's "Text-Book of Medicine," published in 1927, met with unqualified success as a response to an evident demand for an authoritative text covering the entire field of medicine in a single volume After three reprintings, the second edition appears, thoroughly revised, many chapters entirely rewritten and several new chapters added The entire type has been reset A work of this character deserves special mention

There are 135 contributors, each a recognized authority in the particular field which he covers. These are for the most part well known teachers of medicine in medical colleges of American universities, but contributors from Porto Rico, China, the United States Public Health Service, semiprivate sanatoriums and the curator of the New York Zoo have been included, each adding authoritative chapters in some particular field of medical science. Uniformity of style has been sacrificed for authoritative presentation, but save in a few instances this proves of little consequence. As editor, Cecil states in the introduction to the present volume that "it is doubtful if any author of the future will have the temerity to write a complete text-book of medicine without considerable collaboration."

The section on the diseases of the nervous system is edited by Dr. Foster Kennedy. Of this, the chapters on the method of neurologic examination and the diagnostic significance of the cerebrospinal fluid should prove instructive to students. The diseases of the nervous system are presented with sufficient detail and perspective to serve the student's needs.

The book is completely indexed, eighty-nine pages being devoted to this task, which greatly enhances the value of the work as a ready reference treatise.

PERNICIOUS ANEMIA. By LEYBOURNE STANLEY PATRICK DAVIDSON, B.A., M.D., F.R.C.P.E., Lecturer in Systematic and in Clinical Medicine in the University of Edinburgh and GEORGE LOVELL GULLAND, C.M.G., LL.D., M.D., Consulting Physician to the Royal Infirmary, Edinburgh. Appendix on Dietetic Treatment by Ruth Pybus, Sister Dietitian, Royal Infirmary, Edinburgh. Introduction by Lawrence D. Thompson, M.D., Assistant Professor of Clinical Medicine, Washington University School of Medicine. Cloth. Price, \$8.50. Pp. 293, with illustrations. St. Louis: C. V. Mosby Company, 1930.

Because of the great advance in knowledge of pernicious anemia and its treatment, a monograph on the subject is not only warranted but desirable. The recent discovery of liver therapy was not accidental, but came to fruition through painstaking research by many persons which culminated in the experimental treatment, by Whipple and his collaborators, of animals with anemia with a diet of liver and the clinical application of the principles to patients by Minot and Murphy in 1926. In addition to this therapeutic advance, great gains have been made during the past decade in knowledge of the formation of blood, the destruction of blood and the metabolism of pigment. Refined methods in hematology, bacteriology and biochemistry have all added their quota. Unfortunately, this new and useful knowledge has failed to answer many questions concerning the etiology and pathogenicity of the disease but has, on the contrary, opened up many new leads for further research on questions of fundamental importance.

The authors have given a critical review of the literature dealing with every aspect of the disease from the earliest descriptions to the recent fundamental contributions of Peabody, Castle, Minot and Murphy and Sturgis. Chapters are devoted to a historical review, the physiology of the formation and destruction of blood, the pathology, etiology, symptomatology, diagnosis, prognosis and treatment with an appendix on dietotherapy, a bibliography and an index. Excellent discussions appear frequently by writers who have had a large experimental and clinical experience with the disease. The book was written primarily for the specialist, but should be of equal service to the student and the medical practitioner.

UEBER DAS PROBLEM DER BOSARTIGEN GESCHWULSTE. EINE EXPERIMENTELLE UND THEORETISCHE UNTERSUCHUNG. By PROF. DR. LOTHAR HEIDENHAIN. Price, 42 marks. Pp. 229. Berlin: Julius Springer, 1930.

The essence of Dr. Heidenhain's experimental work is the production of neoplasms in mice by the injection of extracts of cancer tissue. The rest of the book also contains elaborate theoretical discussion of the implication of these

experiments and their relation to other theories of the production of cancer. He believes that there is a carcinogenic agent in cancer tissue that has the power to cause the formation of secondary tumors on its injection into animals of different species. The work is excellently illustrated with superb photomicrographs of cancers produced experimentally in mice.

There are, however, insuperable difficulties to the acceptance of this theory. The well known frequency of spontaneous disease in mice is the greatest of these. Sixteen per cent of the animals into which injections were made developed tumors, which is a scarcely greater ratio than one would normally expect in many strains of laboratory mice. There is also the equally well known fact that a large number of totally nonspecific irritations or traumas will produce cancer in mice.

Unless further experimental work can show that the difference between cancers produced by injection and the normal cancer rate in mice is of a far higher degree, one cannot assume that anything has been proved as to the etiology of cancer.

CHRONIC ARTHRITIS AND RHEUMATOID AFFECTIONS—WITH RECOVERY RECORDS. By DR. BERNARD LANGDON WYATT, Director of the Wyatt Clinic, Tucson, Ariz. Price, \$2.50. Pp. 139. New York: William Wood & Company, 1930.

Under this rather ambiguous title, the author has written an account of chronic rheumatism. He presents some dietary fads, recommending a diet with an alkaline ash for rheumatoid arthritis and acid base foods for osteo-arthritis. He overstates the value of colonic lavage, but properly emphasizes the importance of free evacuation from the bowel. He makes the rather common error that viosterol may be substituted for cod liver oil in cases of rheumatoid arthritis. He stresses, and the reviewer believes properly, the importance of climate in the treatment for certain types of chronic arthritis.

In his orthopedic treatment he follows Swaim; this chapter is one of the best.

The volume is written in a popular style and covers the whole field in a satisfactory manner. The general practitioner will find this book helpful, as the methods of treatment are presented concisely.

INTERNATIONAL MEDICAL ANNUAL. A YEAR BOOK OF TREATMENT AND PRACTITIONER'S INDEX. Price, \$6. Pp. 910. New York: William Wood & Company, 1930.

This year's annual is no exception to any of the preceding numbers. It is well condensed and unusually complete considering the amount of subject material to be covered. For the internist, the recent advances in diabetes and peptic ulcers are especially interesting. Various conditions that may be relieved by periaxillary sympathectomy are discussed. Treatment for lobar pneumonia with Felton's concentrated antipneumococcus serum is mentioned in a large series of cases. The treatment for gonorrheal arthritis is thoroughly discussed. As a whole, there are few fields of any importance that have been omitted, including advances in public health. Perhaps the most important feature is in the field of current therapy, which one rarely finds so completely covered in a single volume. As a reference work for the physician, it has its most useful place.

NORMAL, ABSENT AND PATHOLOGIC TONSILS IN YOUNG WOMEN

A COMPARISON OF HISTORIES¹

RUBY L. CUNNINGHAM, M D
BERKELEY, CALIF

A recent government report¹ estimates that about one third of all operations performed since 1924 among the American urban population were for the removal of tonsils and adenoids. In commenting on this statement, the editor of *The Journal of the American Medical Association* pointed out the urgent need for comprehensive statistical studies of the results of the removal of tonsils to date.²

More than one third of the young women entering the University of California during the last ten years had had an operation for the removal of tonsils. As a result of the physical examination required at entrance, about one-third were thought to have normal tonsils, for the remaining one-third, the tonsils were recorded as pathologic, as remnants or as buried or projecting, often without indication of their state of health (table 1).

The opportunity of contrasting the histories of the three groups of women students—those with normal, those with absent and those with pathologic tonsils—gave promise of aiding in the solution of some of the many problems that still surround tonsillectomy.

MATERIAL AND METHOD

The station-to-station method was used for the physical examination required of all students entering the University of California. The histories were taken by nurses, by members of the department of physical education or by older women to whom careful instructions were given. The eyes were examined by an oculist, otorhinologic examinations were made by specialists in that field, the teeth were examined by the dentists of the health service staff, and the general physical examinations were made by physicians. Fortunately, three of the examining physicians have formed the nucleus of the examining staff for the last ten years, thus maintaining a uniformity of standard. It is also fortu-

¹ Submitted for publication, July 29, 1930.

Aided by a grant from the Research Board of the University of California.

¹ Collins, S. D., and Sydenstricker, E. An Epidemiological and Statistical Study of Tonsillitis, Pub. Health Bull., 1927, p. 175.

² Tonsillectomy in the United States, editorial, J. A. M. A. **91** 1195 (Oct. 20) 1928.

nate that the same person has remained the chief of the nose and throat department for this period. Most of the examinations on the nose and throat, however, were made by his associates. The measurements of height, weight, capacity of the chest, estimation of posture and the condition of the feet were made by members of the department of physical education.³ To make possible the tabulation of all histories and physical observations, the information on the entrance examination cards was transferred to punch cards.

The present study is based on the examinations of 14,000 women students entering the University during the last ten years. It was thought best to confine the study to young white women, so cards of oriental and colored students, of persons over 35 years of age and of those on whom important information was lacking were rejected leaving 12,530 to be carefully considered.

TABLE 1—*The Condition of the Tonsils in Relation to Age Incidence*

Condition of Tonsils	15-19 Years		20-24 Years		25-34 Years		35-44 Years	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Normal	2,565	22.23	1,146	36.43	474	33.24	4,185	33.39
Absent	2,756	34.63	914	29.05	464	32.54	4,134	32.99
Pathologic	1,826	22.94	708	22.50	302	21.18	2,836	22.66
Remnants	197	2.48	95	3.02	37	2.59	329	2.62
Buried or projecting	614	7.72	283	9.00	140	10.40	1,046	8.35
Total	7,958	100.00	3,146	100.00	1,426	100.04	12,530	100.01

Accuracy of the Observations and Method—The accuracy of the original history may well be challenged and no doubt suffers as a result of the haste and excitement of the occasion and through the faulty memories of the students. To obtain some idea of the extent of the error from this source, histories were taken a second time from 250 students when they were at ease and had an abundance of time for reflection. Entrance and second histories agreed in incidence of disease in from 85 to 90 per cent of cases, and as to the age of having the disease, to within one year, in from 65 to 85 per cent of cases. The agreement between the two histories for such indefinite items as the occurrence of headache, discharging ears, common colds, constipation, etc., was less, and was probably influenced by recent experiences. The physical examinations and measurements made at the time of entrance to the University were taken seriously by those who performed and recorded them, and probably are fully as accurate as the records of examinations for the army or for insurance.

The cards were punched in an electrically driven machine with a numbered keyboard. With practice, a careful operator makes few

³ A study of the physical observations of those with normal, absent and pathologic tonsils is in progress.

mistakes, and many of these are quickly discovered in the process of sorting and tabulating. The largest number of errors discovered for one hole was 18 in 12,530 cards, or an error of 0.14 per cent. A larger number may have occurred where they could not be detected, but this does not seem probable. Sorting and tabulating in well adjusted machines should be 100 per cent accurate.

Studies were made (1) of all cards, according to the condition of the tonsils, for significant facts in the history and physical examination, (2) of the same facts according to the age groups from 15 to 19, from 20 to 24 and from 25 to 34 years, (3) of the group in which the tonsils were absent for the same facts according to the age groups and as related to the age of the patient when the tonsils were removed.

RELATION OF THE CONDITION OF THE TONSILS TO THE INFECTIOUS DISEASES OF CHILDHOOD

Little has appeared in medical literature to show the relationship between the condition of the tonsils and the incidence of the infectious diseases of childhood. In a recent government bulletin, Collins¹ reported data on measles, mumps, whooping cough, chickenpox, scarlet fever and diphtheria in the children of Hagerstown, Md, and found that "in general, the rates are lowest for the normal, slightly higher for the defective, but considerably higher for the removed group." Zahorsky⁴ thought that his observations showed that the child beginning his school life without tonsils is in greater danger of acute disease than the child who still has them. Hertz⁵ observed 1,185 school children over a period of time and found those with hypertrophied tonsils not any more likely to contract diseases than other children. Crowe, Watkins and Rotholz⁶ pointed out the fact that the tonsils are not the only portal of entry and that organisms pass readily through the mucous membrane of the nose and pharynx.

Michailovitz,⁷ of Russia, collected data on 1,500 children from 1 to 17 years of age and stated "The entire absence of scarlet fever among children whose tonsils and adenoids had been removed, and the appearance of scarlet fever among those who had not undergone removal of them, justifies the conclusion that the removal of hypertrophic tonsils

4 Zahorsky. Tonsillectomy in the Young Child, Interstate M J **26** 67, 1919

5 Hertz, P. Tonsillenhypertrophie bei Schulkindern, Zentralbl f Hals-, Nasen- u Ohrenh **12** 180, 1928

6 Crowe, S J, Watkins, S S, and Rothholz, A S. Relation of Tonsil and Nasopharyngeal Infection to General Systemic Disorders, Bull Johns Hopkins Hosp **28** 1, 1917

7 Michailovitz, N. Materialien zum Tonsillarproblem Zentralbl f Hals-, Nasen- u Ohrenh **13** 147, 1928-1929

and adenoids lowers receptivity for scarlet fever" Jordanof,⁸ of Munich, employed the data available in the University and two medical clinics to solve the question as to whether or not those who have undergone a tonsillectomy are still subject to scarlet fever. Of 362 for whom a questionnaire was returned, 12, or 3.31 per cent, had had scarlet fever in spite of tonsillectomy. In 8 of the 12, remnants of tonsil tissue remained. In 3 of the 12 cases scarlet fever occurred within a period of 3 weeks after operation and may have been of a traumatic nature. Of 110 patients with scarlet fever only 1 had been operated on for removal of the tonsils, since the disease followed the operation promptly, it may also have been traumatic scarlet fever. Zikowsky,⁹ of Vienna, found that among 1,013 patients with scarlet fever only 23 had previously undergone a tonsillectomy. Whether this was due to the fact that persons whose tonsils have been removed are less susceptible to infection with scarlet fever or to the circumstance that only a small percentage of the population of Vienna undergo tonsillectomy could not be ascertained. He considered the tonsils, however, as a portal of entry for scarlet fever, and as a storage room of the virus during the disease. In Kaiser's¹⁰ study of 1,200 tonsillectomized children, the operation was not observed to prevent measles or scarlet fever, but may have lightened the severity of the disease, it seemed, however, to lessen the incidence of diphtheria. In his later publication,¹¹ he stated that 7.6 per cent of the children whose tonsils had been removed contracted scarlet fever, as against 16 per cent of the control group with tonsils. He thought that children whose tonsils had been removed and in whom scarlet fever developed showed considerably less valvular disease of the heart than those with tonsils who contracted scarlet fever. Bloomfield¹² undertook a statistical study of the triad, scarlet fever, follicular tonsillitis and erysipelas, on the basis of 498 questionnaires. He noted that there is a significant, positive association between the susceptibility to acute follicular tonsillitis and to scarlet fever, but that there is no significant association between the susceptibility to tonsillitis and to diphtheria, or between the susceptibility to scarlet fever and to diphtheria. Doull¹³ reported observations on 5,000 white children from

8 Jordanof, K. Gaumentonsillen und Scharlachinfektion, München med Wchnschr **75** 2172 (Dec 21) 1928

9 Zikowsky, I. Tonsillektomie und Scharlach, Wien klin Wchnschr **42** 37 (Jan 10) 1929

10 Kaiser, A. D. Incidence of Infection in Tonsillectomized Children, New York State J Med **25** 469 (March 20) 1925

11 Kaiser, A. D. Incidence of Rheumatism, Chorea and Heart Disease in Tonsillectomized Children, J A M A **89** 2239 (Dec 31) 1927

12 Bloomfield, A. L. Association of Susceptibility to Scarlet Fever and Acute Tonsillitis, California & West Med **28** 477, 1928

13 Doull, J. A. Relationship of Tonsillectomy to Occurrence of Scarlet Fever and Diphtheria, Pub Health Rep **39** 1833 (Aug 1) 1924

5 to 14 years of age, 15 per cent of whom had had their tonsils removed. The observations justified the conclusion that, in the area studied, children whose tonsils had been removed were distinctly less liable to diphtheria, whereas in scarlet fever, no significant difference was shown. Place,¹⁴ who removed tonsils in 122 cases of scarlet fever between the second and the twenty-fourth day of illness, considered tonsillectomy and adenoidectomy as valuable means of shortening the contagiousness of scarlet fever and diphtheria in suitable cases, and that there is reason

TABLE 2—*The Incidence of Illness as Related to the Condition of the Tonsils*

	Normal		Absent		Pathologic		Remnants		Buried or Projecting		Total	
	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent
Measles	3,622	86.59	3,785	91.56	2,478	87.33	300	91.18	924	88.37	11,109	88.66
Mumps	1,959	46.85	2,192	53.02	1,376	48.51	191	58.05	517	49.43	6,235	49.76
Chickenpox	2,474	59.14	2,680	64.83	1,729	60.97	212	64.44	625	59.75	7,720	61.61
Whooping cough	2,692	64.36	2,817	68.14	1,816	64.03	225	68.39	686	65.58	8,236	65.73
Scarlet fever	567	13.55	658	15.92	380	13.40	44	13.37	134	12.81	1,783	14.21
Typhoid fever	163	4.02	164	3.97	120	4.23	12	3.65	55	5.26	519	4.14
Diphtheria	245	5.86	322	7.79	154	5.43	19	5.78	72	6.88	812	6.48
Malaria	159	3.80	188	4.55	123	4.34	13	3.95	60	5.74	543	4.33
Smallpox	165	3.94	139	3.36	121	4.27	13	3.95	48	4.59	486	3.88
Erysipelas	16	0.38	30	0.72	15	0.53	2	0.60	1	0.01	64	0.51
Pneumonia	432	10.32	533	12.89	264	9.31	41	12.46	108	10.32	1,378	11.00
Pleurisy	115	2.74	174	4.21	78	2.75	6	1.82	23	2.20	396	3.16
Chronic colds	219	5.23	293	7.09	133	4.69	13	3.95	61	5.83	719	5.74
Asthma	19	0.45	60	1.45	23	0.81	4	1.22	7	0.67	113	0.90
Hay fever	122	2.92	230	5.56	93	3.28	17	5.17	14	1.34	476	3.80
Influenza	1,500	35.84	2,193	53.05	1,179	41.57	172	52.28	415	39.67	5,459	43.57
Rheumatism	126	3.01	289	6.99	85	3.00	18	5.47	41	3.92	559	4.46
Tonsillitis	915	21.86	1,508	36.48	693	24.44	115	34.95	244	23.33	3,475	27.73
Chorea	16	0.28	38	0.92	13	0.46	2	0.61	2	0.19	71	0.57
Otitis media	163	3.89	255	6.17	67	2.36	15	4.56	36	3.44	536	4.28
Boils	266	6.36	290	7.01	201	7.09	13	3.95	74	7.07	844	6.74
Constipation	338	8.07	419	10.14	231	8.14	32	9.73	114	10.90	1,134	9.05
Appendicitis (with out operation)	156	3.72	270	6.53	93	3.28	16	4.86	33	3.15	568	4.52
Jaundice	106	2.53	127	3.07	73	2.57	6	1.82	30	2.87	342	2.73
Nephritis	5	0.01	9	0.02	1	0.00	2	0.60	1	0.10	18	0.14
Headache	469	11.20	587	14.20	364	12.83	51	15.50	142	13.58	1,613	12.87
Neurasthenia	92	2.19	87	2.10	51	1.09	3	0.91	20	1.91	233	1.86
Neuritis	22	0.52	63	1.52	23	0.81	6	1.82	9	0.86	123	0.98
Insomnia	44	1.04	57	1.38	20	0.71	3	0.91	9	0.86	133	1.06
Tuberculosis	28	0.67	48	1.16	14	0.49	3	0.91	4	0.38	97	0.77
Total	4,185		4,134		2,836		329		1,046		12,530	

to believe that early operations in scarlet fever tend to reduce the danger of complications. Soto,¹⁵ of Spain, reported that diphtheria occurs in much milder form in those whose tonsils have been removed. Stamberger,¹⁶ of Hungary, followed 100 tonsillectomized patients for from one-half to 3 years after the operation, and came to the conclusion that the tendency to scarlet fever and measles remained stationary, but that the

14 Place, E. H. Tonsillectomy in the Contagious Diseases, Boston M. & S. J. **187** 434 (Sept. 21) 1922.

15 Soto, E. F. Indikationen und Kontraindikationen der Mandelextirpation, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **5** 43 1924.

16 Stamberger, I. Ueber die Tonsillenfrage auf Grund von 700 Tonsillektomien, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **10** 386, 1927.

tendency to diphtheria decreased Schick and Topper¹⁷ found that from 60 to 80 per cent of 100 children gave a positive Schick reaction before removal of the tonsils, and that six months after tonsillectomy only 18 per cent gave a positive reaction On the basis of these observations they recommended tonsillectomy instead of immunization with toxin-antitoxin for children with diseased tonsils who are sensitive to horse serum, testing children who have been tonsillectomized six months or more previously before giving toxin-antitoxin

In the present study young women with normal and with pathologic tonsils had had about the same percentage incidence of measles, mumps chickenpox, whooping cough, scarlet fever and diphtheria (table 2 and

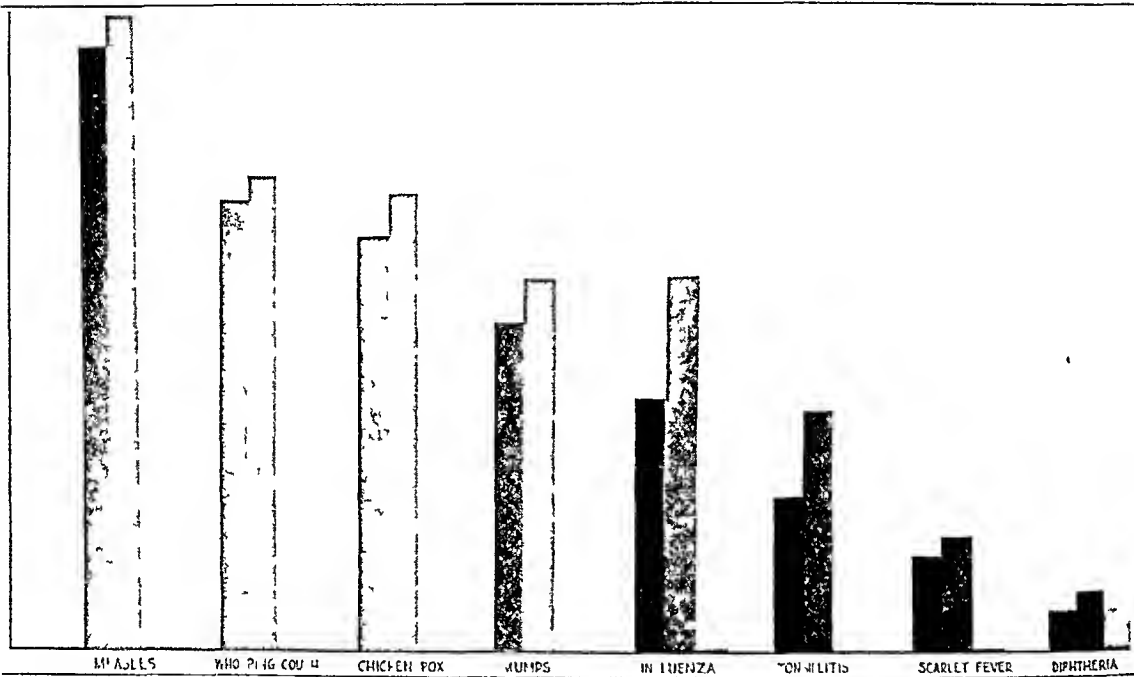


Chart 1—Incidence of measles, whooping cough, chickenpox, mumps, influenza, tonsillitis, scarlet fever and diphtheria, by groups. Scale indicates per cent. In this and chart 2 the black column indicates the group with normal tonsils, the next column those whose tonsils had been removed, and the third column those with pathologic tonsils.

chart 1) In no instance was the difference between percentages statistically significant (i.e., three times the standard error of difference¹⁸) (table 3). Those whose tonsils had been removed gave histories showing a higher percentage of all illnesses than did those with

17 Schick, B, and Topper, A. The Effect of Tonsillectomy on Diphtheria Immunity. *Am J Dis Child* 38:929 (Nov) 1929.

18 The formula used was
Standard error of difference = $\sqrt{\frac{(\% \text{ of A}) (100 - \% \text{ of A})}{\text{Number of A}} + \frac{(\% \text{ of B}) (100 - \% \text{ of B})}{\text{Number of B}}}$
(Yule. *Theory of Statistics*, ed 9, p 269)

normal, or those with pathologic tonsils (table 2 and chart 1) The differences in percentages were consistent and significant for all of the infectious diseases of childhood (table 4)

TABLE 3—*Standard Errors of Difference in Percentage Incidence of Disease and Operations in the Groups with Normal and with Pathologic Tonsils*

Disease or Operation	Tonsils Normal, per Cent	Tonsils Pathologic, per Cent	Difference, per Cent	Standard Error of Difference
Measles	86.59	87.38	0.79	±0.82
Mumps	46.85	48.51	1.66	±1.21
Chickenpox	59.14	60.97	1.83	±1.91
Whooping cough	64.36	64.03	0.33	±1.16
Scarlet fever	13.55	13.40	0.15	±0.83
Diphtheria	5.86	5.43	0.43	±0.56
Pneumonia	10.32	9.31	1.01	±0.72
Common colds	5.23	4.69	0.54	±0.53
Influenza	35.84	41.57	5.73*	±1.18
Rheumatism	3.01	3.00	0.01	±0.42
Tonsillitis	21.86	24.44	2.58	±1.02
Chorea	0.28	0.46	0.18	±0.15
Otitis media	3.89	2.36	1.53*	±0.41
History of cardiac disease	3.23	3.02	0.21	±0.43
Damage to mitral valve	2.05	3.42	1.37	±0.41
Damage to aortic valve	0.54	0.83	0.29	±0.20
Appendectomy	4.73	4.48	0.25	±0.51
Nasal operation	2.03	1.23	0.80	±0.30
Operation on cervical glands	0.57	0.99	0.42	±0.22
Mastoid operation	0.76	0.71	0.05	±0.21
Miscellaneous operations	4.78	3.45	1.33	±0.47

* The difference in these percentages is more than three times the standard error and is therefore statistically significant

TABLE 4—*Standard Error of Difference in Percentage Incidence of Disease and Operation in the Groups with Normal and with Absent Tonsils*

Disease or Operation	Tonsils Normal, per Cent	Tonsils Absent, per Cent	Difference, per Cent	Standard Error of Difference
Measles	86.59	91.56	4.97*	±0.68
Mumps	46.85	53.02	6.17*	±1.38
Chickenpox	59.14	64.83	5.69*	±1.06
Whooping cough	64.36	68.14	3.78*	±1.03
Scarlet fever	13.55	15.92	2.37*	±0.77
Diphtheria	5.86	7.79	1.93*	±0.55
Pneumonia	10.32	12.89	2.57*	±0.70
Common colds	5.23	7.09	1.86*	±0.53
Influenza	35.84	53.05	17.21*	±1.07
Rheumatism	3.01	6.99	3.98*	±0.48
Tonsillitis	21.86	36.48	14.62*	±0.98
Chorea	0.28	0.92	0.64*	±0.17
Otitis media	3.89	6.17	2.28*	±0.48
History of cardiac disease	3.23	5.10	1.87*	±0.44
Damage to mitral valve	2.05	3.45	1.40*	±0.36
Damage to aortic valve	0.54	0.25	0.29	±0.26
Appendectomy	4.73	10.14	5.41*	±0.57
Nasal operation	2.03	4.67	2.64*	±0.39
Operation on cervical glands	0.57	1.79	1.22*	±0.24
Mastoid operation	0.76	1.96	1.20*	±0.25
Miscellaneous operations	4.78	10.37	5.59*	±0.32

* The difference in these percentages is more than three times the standard error and is therefore statistically significant

Scarlet fever and diphtheria (table 2 and chart 1) show much the same relationship in frequency in the three groups as do the less serious infectious diseases of childhood, since those whose tonsils had been removed had a significantly higher incidence of infection with scarlet fever and diphtheria than those with normal tonsils (tables 3 and 4)

From a study of those with absent tonsils, by age groups and with relation to the age when the tonsils were removed evidence seems apparent that the removal of tonsils decreases the incidence of scarlet fever. With the exception of those having their tonsils removed before 5 years of age in the group from 15 to 19 years of age, the earlier the tonsils were removed, the less the total amount of scarlet fever reported (tables 5, 6 and 7 and chart 5). Similar results were not found for measles, mumps, chickenpox or whooping cough, but are found with minor variations and in less degree for diphtheria. It was not found possible to relate these observations to those of other investigators, as data for comparison is limited and as many variations must be taken into account. For instance, records of infections cannot be compared with histories of infections, for obvious reasons. Incidence of infec-

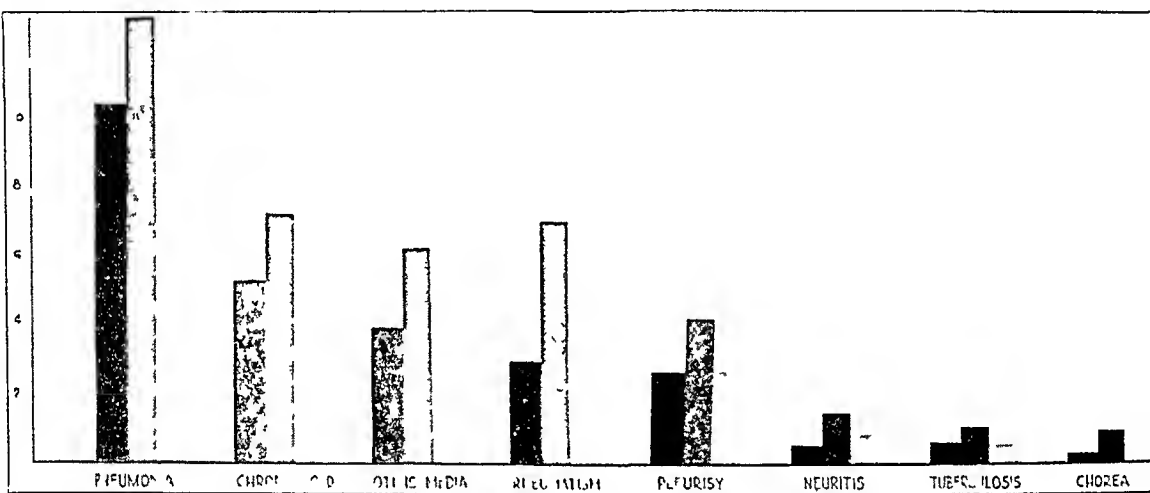


Chart 2—Incidence of pneumonia, chronic colds, otitis media, rheumatism, pleurisy, neuritis, tuberculosis and chorea, by groups. Scale indicates per cent.

tion in thickly populated places cannot be taken as a standard for incidence in places more sparsely populated. The percentages of those having had infectious diseases considered by ages in this study are, on the whole, less than percentages stated by Collins¹⁹ for the same ages and diseases in Eastern and Middle Western areas.

A reasonable explanation of the higher incidence of infectious disease in the group operated on is that the child who is often ill is finally operated on. The higher incidence of illness would be the indication for a tonsillectomy, rather than the absence of tonsils the cause of more frequent infections. The history of infectious diseases cannot, however, be an influential factor in the removal of tonsils of very young children, since among those whose tonsils were removed before the age of

¹⁹ Collins, S. D. Age Incidence of the Common Communicable Diseases of Children, Pub. Health Bull. 44 763 (April 5) 1929.

TABLE 5—The Incidence of Disease Before and After Tonsillectomy in the Group Aged from 15 to 19 Years as Related to Age of Removal

Age of removal	0-4 Years						5-9 Years						10-14 Years						15 Years and Over					
	Before			After			Before			After			Before			After			Before			After		
	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent
Occurrence of disease																								
Disease																								
Measles	21	11.9	141	80.1	498	51.9	393	40.9	756	81.7	95	10.3	340	87.9	9	2.3								
Mumps	10	5.7	77	43.8	199	20.7	288	30.0	382	41.3	101	10.9	186	48.1	9	2.3								
Chickenpox	13	7.4	105	60.0	329	34.3	309	32.2	559	60.4	70	7.6	241	62.3	2	0.5								
Whooping cough	39	22.2	83	47.2	497	51.8	164	17.1	624	67.5	24	2.6	251	64.9	5	1.3								
Scarlet fever	2	1.1	22	12.5	50	5.2	61	6.4	108	11.7	29	3.1	59	15.2	1	0.2								
Typhoid fever	1	0.6	2	1.1	10	1.0	15	1.6	14	1.5	6	0.6	13	3.4	1	0.2								
Diphtheria	3	1.7	6	3.4	29	3.0	17	1.8	51	5.5	16	1.7	28	7.2	1	0.2								
Malaria	0	0.0	5	2.8	6	0.6	23	2.4	35	3.8	10	1.1	24	6.2	2	0.5								
Smallpox	0	0.0	3	1.7	8	0.8	16	1.7	16	1.7	7	0.7	12	3.1	0	0.0								
Flyspelas	1	0.6	1	0.6	2	0.2	1	0.4	4	0.4	4	0.4	2	0.5	0	0.0								
Pneumonia	5	2.8	17	9.7	69	7.2	48	5.0	92	9.9	27	2.9	46	11.9	2	0.5								
Pleurisy	0	0.0	5	2.8	6	0.6	23	2.4	11	1.2	13	1.4	13	3.4	1	1.0								
Chronic colds	2	1.1	9	5.1	22	2.3	16	1.8	22	2.4	27	2.9	21	5.1	11	3.6								
Asthma	0	0.0	6	3.4	3	0.3	10	1.0	9	1.0	3	0.3	4	1.0	1	0.3								
Hay fever	3	1.7	11	6.2	3	0.3	37	3.8	10	1.1	35	3.8	9	2.3	12	3.1								
Influenza	1	0.6	99	56.2	45	4.7	465	48.4	172	18.6	333	36.0	172	44.4	54	14.0								
Rheumatism	1	0.6	4	2.3	8	0.8	16	1.7	28	3.0	20	2.2	12	3.1	8	2.1								
Tonsillitis	32	18.2	6	3.4	236	24.6	24	2.5	338	36.5	12	1.3	191	49.4	3	0.8								
Chorea	0	0.0	2	1.1	1	0.1	4	0.4	7	0.8	2	0.2	4	1.0	0	0.0								
Otitis media	4	2.3	11	6.2	19	2.0	38	4.0	30	3.2	27	2.9	18	4.6	1	0.2								
Total number	176		176		960		960		925		925		387		387									

TABLE 6—*The Incidence of Disease Before and After Tonsillectomy in the Group Aged from 20 to 24 Years as Related to the Age of Removal*

Age of removal Occurrence of disease Disease	0-4 Years						5-9 Years						10-14 Years						15 Years and Over					
	Before			After			Before			After			Before			After			Before			After		
	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent
Measles	1	18.1	16	72.7			78	48.8	76	47.5			167	78.4	25	11.7	369	89.1	9	2.2				
Mumps	1	1.5	10	45.1			32	20.0	54	33.8			92	13.2	23	10.8	239	55.3	6	1.1				
Chickenpox	2	9.1	12	51.6			58	36.2	44	27.5			101	17.1	26	12.2	261	63.0	5	1.2				
Whooping cough	3	13.6	7	31.8			89	55.6	29	18.1			112	66.7	6	2.8	281	68.6	1	0.2				
Scarlet fever	0	0.0	2	9.1			6	3.8	11	6.9			29	13.6	2	0.9	81	20.3	6	1.1				
Typhoid fever	0	0.0	3	13.6			1	2.5	7	4.4			7	3.2	2	0.9	19	4.6	0	0.0				
Diphtheria	1	4.5	1	4.5			11	8.8	6	3.8			16	7.5	2	0.9	18	11.6	1	0.2				
Mal aria	0	0.0	0	0.0			1	0.6	3	1.9			3	1.1	3	1.1	20	1.8	1	0.7				
Smallpox	0	0.0	1	4.5			2	1.2	1	0.6			8	3.8	2	0.9	18	4.4	1	1.0				
Erysipeloid	1	4.5	2	9.1			10	6.4	11	8.8			0	0.0	1	0.5	2	0.5	2	0.5				
Pneumonia	1	4.5	0	0.0			9	5.6	0	0.0			5	2.1	1	1.1	6	1.5	16	3.9				
Pleurisy	1	4.5	0	0.0			9	5.6	5	3.0			5	2.1	1	1.1	12	2.9	21	5.8				
Chronic colds	1	4.5	0	0.0			1	2.5	2	1.2			1	0.5	2	0.9	2	0.5	3	0.7				
Asthma	0	0.0	0	0.0			23	14.4	2	1.2			12	5.6	5	2.4	11	2.7	15	3.6				
Hay fever	0	0.0	1	4.5			71	44.4	5	3.1			72	33.8	22	10.3	61	15.5	161	39.6				
Influenza	11	55.1	1	4.5			5	3.1	0	0.0			8	3.8	8	3.8	5	1.2	26	6.1				
Rheumatism	0	0.0	0	0.0			11	8.8	12	25.2			1	1.1	72	33.8	2	0.5	232	56.1				
Tonsillitis	1	4.5	2	9.1			0	0.0	1	0.6			3	1.4	2	0.9	0	0.0	6	1.4				
Chorea	0	0.0	0	0.0			4	2.5	2	1.2			3	1.4	8	3.8	6	1.1	30	7.2				
Otitis media	2	9.1	1	4.5																				
Total number	22		22				160		160				213		213		111		414					

TABLE 7—The Incidence of Disease Before and After Tonsillectomy in the Group Aged from 25 to 34 Years as Related to the Age of Removal

Age of removal Occurrence of disease	0-4 Years						5-9 Years						10-14 Years						15 Years and Over					
	Before			After			Before			After			Before			After			Before			After		
	Num ber	Per Cent	Per Cent	Num ber	Per Cent	Per Cent	Num ber	Per Cent	Per Cent	Num ber	Per Cent	Per Cent	Num ber	Per Cent	Per Cent	Num ber	Per Cent	Per Cent	Num ber	Per Cent	Per Cent	Num ber	Per Cent	Per Cent
Measles	0	0.0	0.0	0	0.0	0.0	5	71.4	28.6	2	28.6	0.0	16	72.7	9.1	2	9.1	0.0	287	89.4	8	2.5	0.0	0.0
Mumps	0	0.0	0.0	0	0.0	0.0	2	28.6	28.6	2	28.6	0.0	8	36.4	22.7	5	22.7	0.0	186	57.9	8	2.5	0.0	0.0
Chickenpox	0	0.0	0.0	0	0.0	0.0	3	42.8	42.8	3	42.8	0.0	5	22.7	22.7	5	22.7	0.0	211	65.7	1	0.0	0.0	0.0
Whooping cough	0	0.0	0.0	0	0.0	0.0	3	42.8	0.0	0	0.0	0.0	6	27.3	18.2	4	18.2	0.0	206	61.2	2	0.6	0.0	0.0
Scarlet fever	0	0.0	0.0	0	0.0	0.0	1	12.8	28.6	2	28.6	0.0	4	18.2	1.5	1	1.5	0.0	79	24.6	6	1.9	0.0	0.0
Typhoid fever	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	5	22.7	9.1	2	9.1	0.0	27	8.4	3	0.9	0.0	0.0
Diphtheria	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	6	27.3	4.5	1	4.5	0.0	36	11.2	1	0.0	0.0	0.0
Malaria	0	0.0	0.0	0	0.0	0.0	0	0.0	11.3	1	11.3	0.0	0	0.0	0.0	0	0.0	0.0	15	4.7	2	0.6	0.0	0.0
Smallpox	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	24	7.5	0	0.0	0.0	0.0
Erysipelas	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	4	1.2	1	0.3	0.0	0.0
Pneumonia	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	1	4.5	22.7	5	22.7	0.0	42	13.1	3	0.9	0.0	0.0
Pleurisy	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	17	5.3	10	3.1	0.0	0.0
Chronic colds	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	1	4.5	1.5	1	1.5	0.0	20	6.2	8	2.5	0.0	0.0
Asthma	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	1	0.3	3	0.9	0.0	0.0
Hay fever	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	0	0.0	1.5	1	1.5	0.0	10	3.1	6	1.9	0.0	0.0
Influenza	0	0.0	0.0	0	0.0	0.0	0	0.0	12.8	3	12.8	0.0	1	4.5	27.3	6	27.3	0.0	111	34.6	67	20.9	0.0	0.0
Rheumatism	0	0.0	0.0	0	0.0	0.0	0	0.0	14.3	1	14.3	0.0	0	0.0	0.0	0	0.0	0.0	27	8.4	6	1.9	0.0	0.0
Tonsillitis	0	0.0	0.0	0	0.0	0.0	0	0.0	14.3	1	14.3	0.0	9	40.9	4.5	1	4.5	0.0	162	50.5	5	1.6	0.0	0.0
Chorea	0	0.0	0.0	0	0.0	0.0	0	0.0	14.3	1	14.3	0.0	0	0.0	0.0	0	0.0	0.0	1	0.3	0	0.0	0.0	0.0
Otitis media	0	0.0	0.0	0	0.0	0.0	0	0.0	11.3	1	11.3	0.0	2	9.1	1.5	1	1.5	0.0	18	5.6	3	0.9	0.0	0.0
Total number	0			0			7			7			22			22			321		321			

TABLE 8—*Normal Tonsils History of Illness by Age Groups*

	15 19 Years		20 24 Years		25 34 Years		15 34 Years	
	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent
Measles	2,168	84.52	1,023	89.27	431	90.93	3,622	86.59
Mumps	1,117	43.55	571	49.82	271	57.17	1,959	46.85
Chickenpox	1,504	58.64	682	59.51	288	60.76	2,474	59.14
Whooping cough	1,642	64.02	740	64.57	310	65.40	2,692	64.36
Scarlet fever	284	11.07	179	15.62	104	21.94	567	13.55
Typhoid fever	70	2.73	61	5.32	37	7.81	168	4.02
Diphtheria	122	4.76	84	7.33	39	8.23	245	5.86
Malaria	87	3.39	49	4.28	23	4.85	159	3.80
Smallpox	82	3.20	60	5.24	23	4.85	165	3.94
Erysipelas	9	0.35	2	0.17	5	1.05	16	0.38
Pneumonia	238	9.28	129	11.25	65	13.71	432	10.32
Pleurisy	47	1.83	32	2.79	36	7.59	115	2.74
Chronic colds	125	4.87	67	5.85	27	5.70	219	5.23
Asthma	9	0.35	6	0.52	4	0.84	19	0.45
Hay fever	63	2.46	38	3.32	21	4.43	122	2.92
Influenza	891	34.73	422	36.82	187	39.45	1,500	35.84
Rheumatism	68	2.65	38	3.32	20	4.22	126	3.01
Tonsillitis	495	19.30	289	25.22	131	27.64	915	21.86
Chorea	9	0.35	3	0.26	4	0.84	16	0.28
Otitis media	93	3.62	48	4.19	22	4.64	163	3.89
Boils	168	6.55	64	5.58	34	7.17	266	6.36
Constipation	159	6.20	107	9.34	72	15.19	338	8.07
Appendicitis	73	2.85	58	5.06	25	5.27	156	3.72
Jaundice	54	2.11	30	2.62	22	4.64	106	2.53
Nephritis	4	0.16	1	0.09	0	0.00	5	0.01
Headaches	292	11.38	127	11.08	50	10.55	469	11.20
Neurasthenia	37	1.44	29	2.53	26	5.48	92	2.19
Neuritis	7	0.27	6	0.52	9	1.90	22	0.52
Insomnia	11	0.43	20	1.74	13	2.74	44	1.04
Tuberculosis	10	0.39	9	0.78	9	1.90	28	0.67
Total	2,365		1,146		474		4,185	

TABLE 9—*Absent Tonsils History of Illness by Age Groups*

	15 19 Years		20 24 Years		25 34 Years		15 34 Years	
	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent
Measles	2,529	91.76	832	91.03	424	91.38	3,785	91.56
Mumps	1,412	51.23	513	56.13	267	57.54	2,192	53.02
Chickenpox	1,819	66.00	568	62.14	293	63.15	2,680	64.83
Whooping cough	1,901	68.93	625	68.38	291	62.72	2,817	68.14
Scarlet fever	377	13.68	161	17.61	120	25.86	658	15.92
Typhoid fever	71	2.58	44	4.81	49	10.56	164	3.97
Diphtheria	171	6.20	101	11.05	50	10.78	322	7.79
Malaria	123	4.46	57	6.05	28	6.03	188	4.55
Smallpox	69	2.50	42	4.60	28	6.03	139	3.36
Erysipelas	18	0.65	7	0.76	5	1.08	30	0.72
Pneumonia	340	12.34	124	13.57	69	14.87	533	12.89
Pleurisy	89	3.23	44	4.81	41	8.84	174	4.21
Chronic colds	178	6.46	68	7.44	47	10.13	293	7.09
Asthma	39	1.42	15	1.64	6	1.29	60	1.45
Hay fever	133	4.82	73	7.99	24	5.17	230	5.56
Influenza	1,486	53.92	460	50.33	247	53.23	2,193	53.05
Rheumatism	112	4.06	60	6.56	46	9.91	289	6.99
Tonsillitis	893	32.40	388	42.45	227	48.92	1,508	36.48
Chorea	23	0.83	13	1.42	2	0.43	38	0.92
Otitis media	164	5.95	59	6.46	32	6.90	255	6.17
Boils	191	6.93	58	6.34	41	8.84	290	7.01
Constipation	219	7.95	119	13.12	81	17.46	419	10.14
Appendicitis	159	5.77	68	7.44	43	9.27	270	6.53
Jaundice	75	2.72	31	3.39	21	4.52	127	3.07
Nephritis	4	0.14	2	0.22	3	0.65	9	0.02
Headaches	396	14.37	128	14.00	63	13.58	587	14.20
Neurasthenia	43	1.56	26	2.84	18	3.88	87	2.10
Neuritis	24	0.87	20	2.19	19	4.09	63	1.52
Insomnia	18	0.65	19	2.08	20	4.31	57	1.38
Tuberculosis	24	0.87	11	1.20	13	2.80	48	1.16
Total	2,756		914		464		4,134	

5 years in the group from 15 to 19 years of age (tables 5 6 and 7 and chart 5), considerably more than 50 per cent had not had measles, mumps, chickenpox or whooping cough before operation. When the factors of age and epidemic cycles are taken into account as much as is possible by considering the persons in age groups, the same general greater incidence of infectious disease in the absent tonsil group is apparent (tables 8, 9 and 10 and chart 3). A study of whether the infection preceded or followed the tonsillectomy should prove helpful,

TABLE 10—*Pathologic Tonsils History of Illness by Age Groups*

	15-19 Years		20-24 Years		25-34 Years		15-34 Years	
	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent
Measles	1,576	86.31	631	89.12	271	88.74	2,478	87.38
Mumps	855	46.82	361	50.99	160	52.98	1,376	48.51
Chickenpox	1,124	61.56	424	59.89	181	59.93	1,729	60.97
Whooping cough	1,162	63.64	470	66.38	184	60.93	1,816	64.03
Scarlet fever	215	11.77	111	15.68	54	17.88	380	13.40
Typhoid fever	55	3.01	30	4.24	35	11.59	120	4.23
Diphtheria	97	5.31	40	5.65	17	5.63	154	5.43
Malaria	76	4.16	23	3.25	24	7.95	123	4.34
Smallpox	70	3.83	32	4.52	19	6.29	121	4.27
Erysipelas	7	0.38	4	0.56	4	1.32	15	0.53
Pneumonia	156	8.54	71	10.03	37	12.25	264	9.31
Pleurisy	40	2.19	20	2.82	18	5.96	78	2.75
Chronic colds	72	3.94	42	5.93	19	6.29	133	4.69
Asthma	16	0.88	6	0.85	1	0.33	23	0.81
Hay fever	58	3.18	25	3.53	10	3.31	93	3.28
Influenza	750	41.07	305	43.08	124	41.06	1,179	41.57
Rheumatism	47	2.57	25	3.53	13	4.30	85	3.00
Tonsillitis	437	23.93	174	24.58	82	27.15	693	24.44
Chorea	5	0.27	6	0.85	2	0.66	13	0.46
Otitis media	34	1.86	23	3.25	10	3.31	67	2.36
Boils	127	6.96	50	7.06	24	7.95	201	7.09
Constipation	129	7.06	64	9.04	38	12.58	231	8.14
Appendicitis	50	2.74	28	3.94	15	4.97	93	3.28
Jaundice	42	2.30	17	2.40	14	4.64	73	2.57
Nephritis	1	0.05	0	0.00	0	0.00	1	0.04
Headaches	241	13.20	88	12.43	35	11.59	304	12.83
Neurasthenia	12	0.66	11	1.55	8	2.65	31	1.09
Neuritis	12	0.66	6	0.85	5	1.66	23	0.81
Insomnia	2	0.11	5	0.71	13	4.30	20	0.71
Tuberculosis	5	0.27	6	0.85	3	0.99	14	0.49
Total	1,826		708		302		2,836	

but fails in much of its purpose, as no figures have been found with which satisfactory comparisons can be made, despite the abundant information of the recent government report¹⁹ on the age incidence of communicable diseases.

There seems to be no general agreement as yet as to the effect of the condition of the tonsils on the incidence of the infectious diseases of childhood. The literature is contradictory and confusing. If the explanation that the child who is often ill ultimately has his tonsils removed is accepted for the slightly higher percentages of all illnesses in the group with absent tonsils, the present study does not necessarily indicate an interdependent relationship between the condition of the tonsils and the percentage of incidence of measles, mumps, whooping cough and chickenpox. However, there seems to be a slightly beneficial effect of

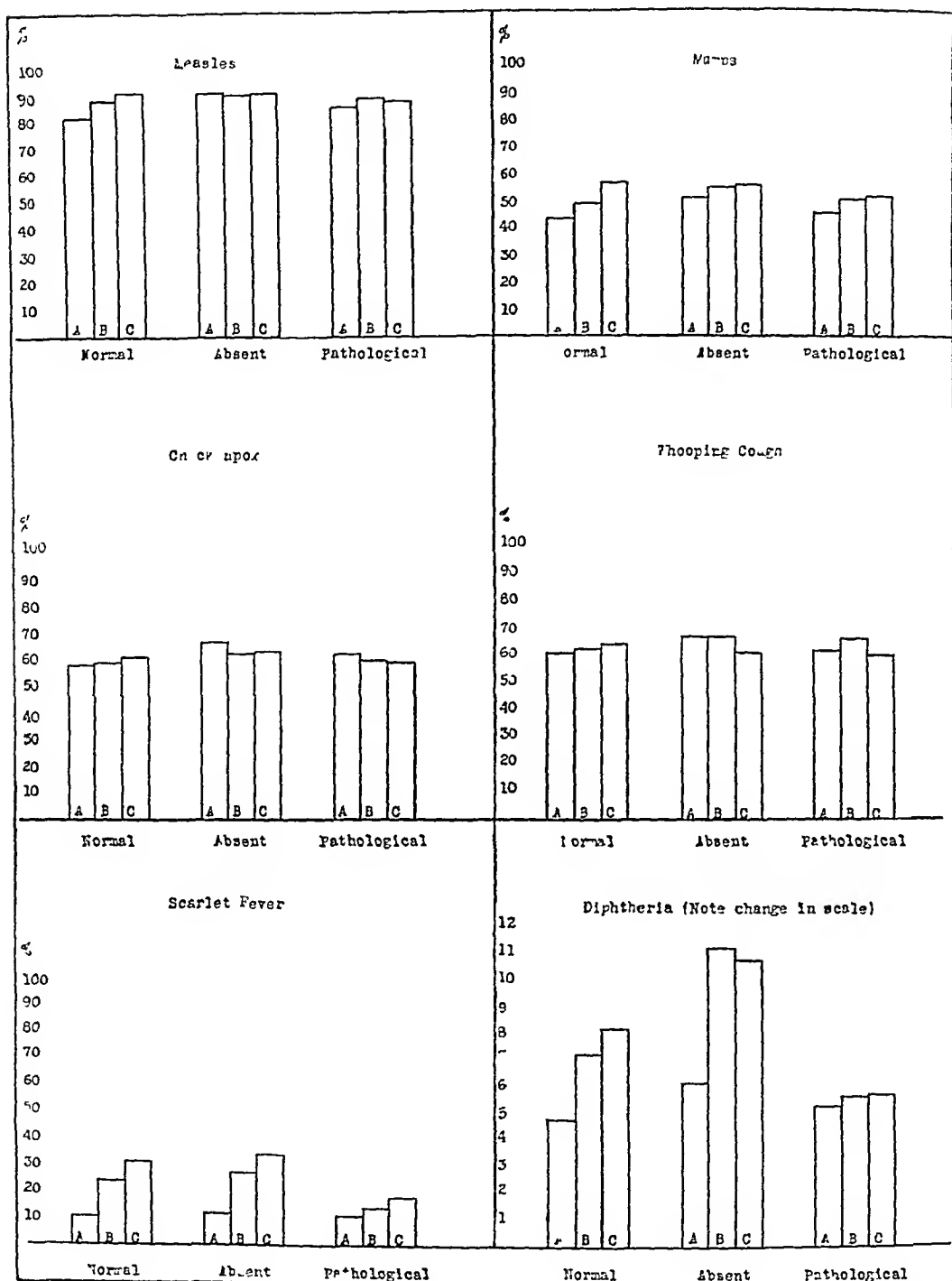


Chart 3—Incidence of infectious diseases according to age and the condition of the tonsils. In this and chart 4, *A* indicates the group from 15 to 19 years (2,565 with normal tonsils, 2,756 whose tonsils had been removed and 1,826 with pathologic tonsils), *B*, those from 20 to 24 years (1,146 with normal tonsils, 914 whose tonsils had been removed and 708 with pathologic tonsils), *C*, those from 25 to 34 years (476 with normal tonsils, 464 whose tonsils had been removed and 302 with pathologic tonsils).

early tonsillectomy on the susceptibility to scarlet fever and to diphtheria. The last mentioned point needs confirmation from larger groups of subjects before its final acceptance.

RELATION TO DISEASES OF THE RESPIRATORY TRACT

As a result of a questionnaire study of 529 persons who had had their tonsils removed, Coakley and Pratt²⁰ thought that a well performed tonsillectomy and adenoidectomy caused a marked lessening of the acute infections of the upper respiratory tract. Soto¹⁵ stated that tonsillectomized children are less subject to catarrhal or general infections than children with tonsils. Treen²¹ advocated the removal of tonsils for "recurrent catarrh of the nose and throat." Although Stoker²² raised an objection to the removal of normal tonsils, he advises their removal for chronic rhinitis or sinusitis and for repeated colds and sore throats. Pond²³ discussed the possibility of infected tonsils causing sinusitis, and of sinusitis resulting in tonsillitis, and gave figures to show that "tonsillectomy in adults does cure a few infected sinuses, and improves many." Kaisei¹⁰ followed 1,200 children for a period of 3 years after tonsillectomy, and found that the operation did not influence infections of the larynx, bronchi and lungs. However, in a second article,¹¹ contrasting the 1,200 children operated on with 1,200 for whom the operation was advised but not performed, he stated "Frequent head colds relieved in 75 per cent of the cases offers a definite cause for the removal of tonsils and adenoids." In reviewing histories of 12,000 colds in 5,000 Yale students, Smiley²⁴ stated "Since removal of nasal obstructions and diseased tonsils in more than half of those having 'four or more' colds a year has not resulted in a reduction of the frequent colds, it seems fair to conclude that nasal obstructions and diseased tonsils are not major factors in the majority of persons suffering with frequent colds." Forsythe²⁵ found for 537 "students of the University of Michigan who had had their tonsils removed 40 per cent more acute respiratory infections than for those who have not been

20 Coakley, C. G., and Pratt, E. L. Analysis of the Systemic and Local Conditions Following Tonsillectomy and Adenoidectomy, *Laryngoscope* **32** 82, 1922.

21 Treen, Jozsef. Ueber das Tonsillenproblem und die Bakteriennvasion ueber die Luftwege, *Zentralbl. f. Hals-, Nasen- u. Ohrenh.* **12** 180, 1928.

22 Stoker, Fred. The "Tonsil" Question, *Lancet* **2** 1125 (Nov. 26) 1927.

23 Pond, C. W. Some End Results of Tonsillectomy, with Special Reference to Sinus Infection in Adults, *Laryngoscope* **40** 286, 1930.

24 Smiley, D. F. A Study of the Acute Infections of the Throat and Respiratory System, *J. A. M. A.* **82** 540 (Feb. 16) 1924.

25 Forsythe, W. E. Health Record of University Students as Related to Tonsillectomy, *Pub. Health Rep.* **43** 560 (March 9) 1928.

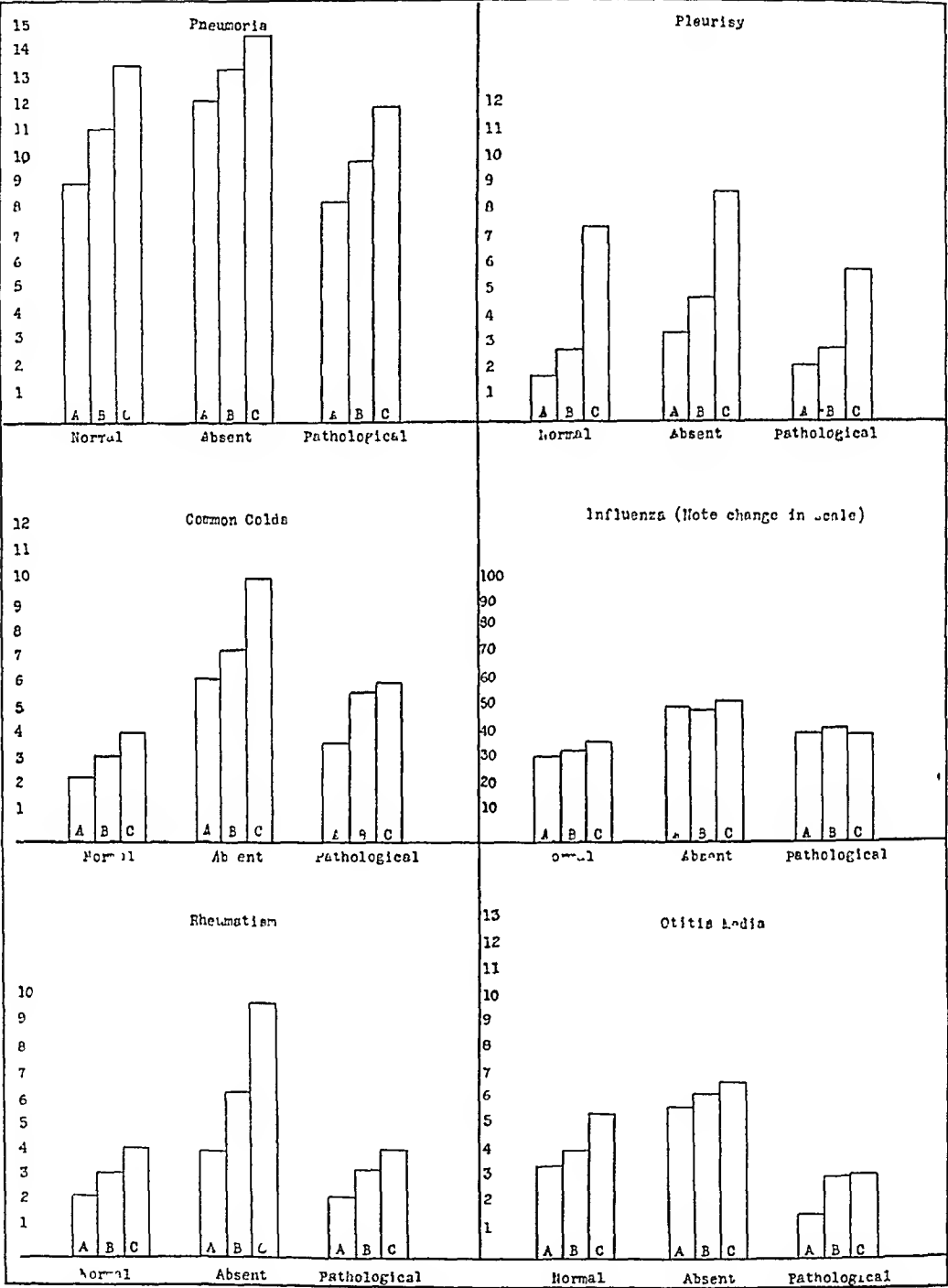


Chart 4—Incidence of infections of the respiratory tract, according to age and the condition of the tonsils

favoired with the surgeon's knife" Norsk²⁶ observed that when catching a cold after a tonsillectomy patients seem to be subject to attacks of acute pharyngitis, and he suspected that this tendency may have been present before operation and its symptoms obscured by the far more serious ones pertaining to tonsillitis

The incidence of pneumonia, pleurisy, chronic colds and tuberculosis differs only slightly in the normal tonsil and pathologic tonsil groups, while their incidence is greater among those whose tonsils had been removed than among those of the other two groups (tables 2, 3 and 4 and chart 2) Here, as well as in the case of infectious diseases of childhood, the observations remain consistent when considered by age groups (tables 8, 9 and 10 and chart 4) Probably the same explanation holds for the slightly greater frequency of the history of respiratory illness as for the greater frequency of infectious diseases in the absent tonsil group The child who is often ill is apt ultimately to be operated on

The answer to the question, "Are you subject to colds?" would, in most instances, be answered on the basis of recent experience and would seem to indicate that the removal of tonsils is not an entirely satisfactory method of preventing infections of the upper respiratory tract, since 7.09 per cent of those whose tonsils had been removed gave a history of frequent colds and only 5.23 per cent of those with normal tonsils and 4.69 per cent of those with pathologic tonsils gave a similar history According to these figures, there is little argument for removing pathologic tonsils to lessen the incidence of the ordinary infections of the respiratory tract, since the subjects with pathologic tonsils had fewest colds There is, however, more chance than reliability in the slight difference in percentages between those with normal, and those with pathologic tonsils

In the literature there is much the same contradiction and confusion relative to the effect of the condition of the tonsils on the occurrence of infection of the respiratory tract as on the frequency of infectious diseases of childhood If the explanation that the child with many infections of the respiratory tract ultimately has his tonsils removed is accepted to account for the universally higher percentage of infections of the respiratory tract in the group whose tonsils are absent than in the group with normal tonsils or the group with pathologic tonsil, this study shows no significant relationship between the condition of the tonsils and the incidence of infections of the respiratory tract

Local infections of the tonsillar tissue, with or without peritonsillar abscess or hyperplasia of Waldeyer's ring, interfering with deglutition or respiration, undoubtedly furnished the indication for operations on

²⁶ Norsk, Frans Ergebnisse der Tonsillektomie bei Erwachsenen, Ztschr f Hals-, Nasen- u Ohrenh 2 294, 1922

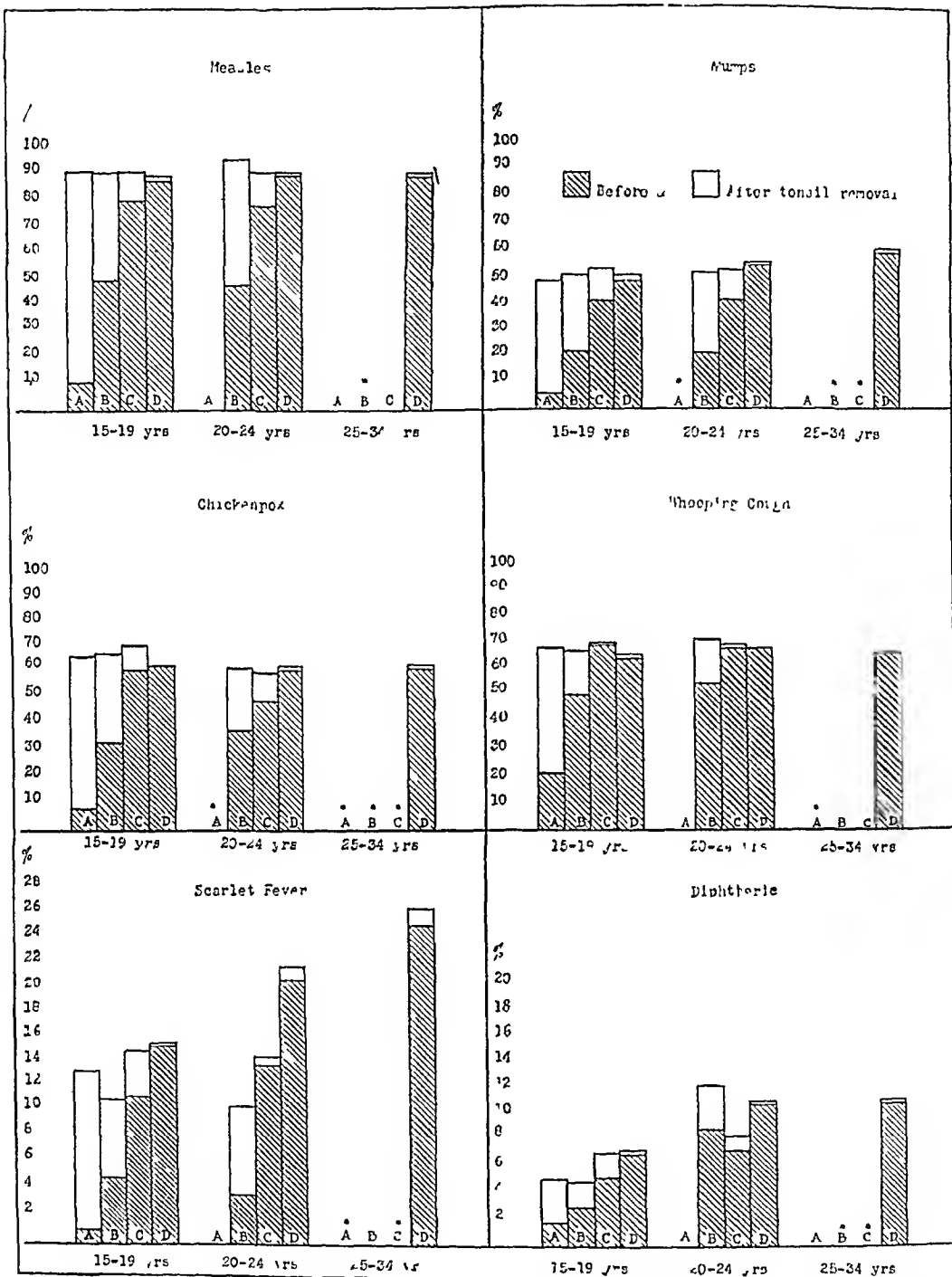


Chart 5—Incidence of infectious diseases before and after tonsillectomy, according to age and the year when the tonsils were removed. In this and chart 6, *A* indicates those whose tonsils were removed before 5 years of age (176 in the 15 to 19 age group, 22 in the 20 to 24 age group and 0 in the 25 to 34 age group), *B*, those whose tonsils were removed between 5 and 10 years of age (960 in the 15 to 19 age group, 160 in the 20 to 24 age group and 7 in the 25 to 34 age group), *C*, those whose tonsils were removed between 10 and 15 years of age (925 in the 15 to 19 age group, 213 in the 20 to 24 age group and 22 in the 25 to 34 age group), *D*, those whose tonsils were removed after 15 years of age (387 in the 15 to 19 age group, 414 in the 20 to 24 age group and 321 in the 25 to 34 age group). The asterisks indicate that the data were insufficient to justify graphic representation.

the tonsils in early times. That operation for the removal of tonsillar tissue ranks with the oldest of operations and has been practiced throughout the ages is evident by the fact that Hindu physicians²⁷ advocated the removal of the tonsils as early as 1000 B. C., advising that they be seized with forceps and cut with a semicircular knife. Hippocrates advised opening tonsillar abscesses, but did not speak of removal of the tonsils. Celsus probably initiated finger dissection, as he suggested that tonsils that remain indurated after inflammation be disengaged all around with the finger and pulled out. Galen described a snare for amputation, and some mention of the operation sounds as if it were an ordinary practice of his day. Peter Lowe, founder of the School of Medicine of Glasgow, published a book in 1634 in which he described (1) opening tonsillar abscesses, (2) tracheotomy for suffocation from enlarged tonsils, (3) removal of tonsils by snare, (4) by cautery and (5) by pulling away with crossets.

Wiseman²⁸ described removal of the tonsils by making a ligature about their base and snipping them off with a pair of crooked probe scissors.

The remarks of Samuel Sharp,²⁹ surgeon at Guy's Hospital from 1733 to 1757, on removal of the tonsils are quaint and worthy of repetition, since they contain some elements of thought that have long occupied the minds of physicians, and hint at others that are under discussion at the present moment.

Besides there is no operation in surgery that, in my opinion, ought to give an operator so much encouragement. It is neither dreadful in the doing nor melancholy in the event. The patient has always been restored to a perfect and lasting health.

The continued good success attending this operation is an answer to the common objection that has formerly been made to it, and perhaps may still be an objection with some foreigners, that it must be dangerous to destroy a part by which nature has been accustomed to fling off any disorder of the constitution, left for want of a discharge, the humour continuing to (circulate) float in the blood, should produce a fever or some other ill habit of the body. It was thought that the frequent accidental inflammation of scirrhus tonsils are not to be considered as local disorders, but like the gout, a distemper in the constitution, which must be received on some one part for the good of the whole. However, the absolute exemption from future inflammatory disorders, in consequence of the operation, seems to demonstrate that the weakness of the part is the chief cause of the complaints.

Local infections of tonsillar tissue, with or without tonsillar abscess, continue to be listed and generally accepted as indications for removal.

²⁷ Mollison, W. M. *Work of Samuel Sharp and His Predecessors on Function and Surgery of Tonsils*, Guy's Hosp. Rep. **78** 93, 1928.

²⁸ Wiseman, Richard. *Severall Chirurgicall Treatises*, ed. 5. London, B. Tooke, 1719.

²⁹ Sharp, Samuel. *Critical Enquiry into the Present State of Surgery*, London, J. & R. Torsin, 1750.

of the tonsils. On this point there seems to be little argument when relief of the local condition is the object of the operation.

Almost 28 per cent of all students entering the University of California gave a history of having had tonsillitis (table 2). The difference between the percentage of those with normal tonsils giving a history of tonsillitis and those with pathologic tonsils giving a similar history is less than might be expected. There were 21.86 per cent of the former and 24.44 per cent of the latter, with a difference of only 2.58 per cent ± 1.02 . The difference between the percentage of those whose tonsils had been removed (36.48 per cent) and those with normal tonsils (21.86 per cent) giving a history of tonsillitis is, in contrast, considerable 14.62 per cent ± 0.98 . It is not surprising that those whose tonsils had been removed gave a history of an attack of tonsillitis since the local inflammation of the tissue, especially if recurrent, is considered by most physicians a definite indication for its removal.

RELATIONS TO OTITIS MEDIA

Many textbooks influential in shaping the opinions of members of the medical profession give recurrent infections of the ear, or chronic aural discharge as a definite indication for tonsillectomy. Some recommend the operation as a prophylactic measure against otitis media. Crowe, Watkins and Rothholz,⁶ basing their conclusions on 1,000 cases of tonsillectomy at Johns Hopkins Hospital during the 5 years preceding 1917, gave otitis media and eustachian salpingitis as indications for tonsillectomy. Rojas,³⁰ of Spain found 44 per cent of 4,266 school children with enlarged tonsils and a diminution in hearing. Eight months after tonsillectomy, only 12 per cent remained hard of hearing. Treen,²¹ of Hungary, advised tonsillectomy for recurrent infection of the middle ear. Van der Hoeven,³¹ of Holland, considered that improvement occurred in 80 per cent of 902 patients operated on for removal of the tonsils, including 42 patients with infection of the middle ear. Kaiser¹¹ followed 1,200 children for 3 years after tonsillectomy, and stated that the operation lessened the chances of a discharge from the ear. Cummings³² gave deafness in children and chronic aural discharge as indications for tonsillectomy. Love,³³ basing his judgment on 4,000 patients operated on, considered both deafness and a discharge

30 Rojas F. A. Mandelhypertrophie und Adenoide in der Schule, Zentralbl f Hals-, Nasen- u Ohrenh **12** 755, 1928.

31 van der Hoeven, L. J. Bemerkungen im Anschluss an 3,300 Halsoperationen bei Kindern. Zentralbl f Hals-, Nasen- u Ohrenh **7** 231 1925.

32 Cummings, G. O. Why Remove Tonsils and Adenoids? M. J. & Rec **128** 201 (Sept 5) 1928.

33 Love J. K. Tonsillectomy in School Clinics, J. Laryng & Otol **39** 135, 1924.

from the middle ear as arguments for removal of the tonsils. Wagers³⁴ followed 247 patients after removal of the tonsils, and in conclusion considered aural discharge an indication for operation. Stokes,³² although warning against needless operation, included suppuration of the ears as an indication. Ingersoll³⁵ reported on a survey of the school children of Rochester, N. Y., in which 23,000 of 58,000 were listed as having markedly hypertrophied or badly infected tonsils slated for removal. As a result of the campaign, 8,000 children between the ages of 2 and 16 had tonsils removed during a period of 3 months. Following the operations there were 30 cases of acute purulent otitis media, none of which went on to mastoiditis. Collins¹ found diseases of the ear lowest among children with normal tonsils, higher among those with defective tonsils and highest among those whose tonsils had been removed. Paton,³⁶ of England, in considering the histories and observations of 424 girls between the ages of 13 and 15 years found that children operated on not only are not benefited but, on the contrary, are in worse condition and that removal of the tonsils and adenoids causes a more frequent appearance of running ears than in the control group.

Since otitis media is commonly considered as an urgent indication for the removal of tonsils, it is not surprising to find that a large number of those whose tonsils were absent had a history of aural infection (table 2 and chart 2). No doubt, in many instances the aural infection preceded the removal of the tonsils. The presence of pathologic tonsils does not seem to predispose a patient to aural infection since those with normal tonsils had a significantly higher percentage of otitis media than those with pathologic tonsils (tables 3 and 4). When one considers the number of cases of disease of the ear preceding and following tonsillectomy at various ages (table 5), the arguments in favor of removing the tonsils as a prophylaxis against aural infection are not convincing. In the group from 15 to 19 years of age the earlier the tonsils were removed the higher was the total incidence of otitis media. In the group from 20 to 24 years of age the relation of the age of operation to the total number of cases of otitis media is reversed, the earlier the operation, the less the total involvement of the ear. The fact that half the cases of aural infection followed, rather than preceded, tonsillectomy in the groups from 15 to 19 and from 20 to 24, years of age when the tonsils were removed

34 Wagers A. J. Study of Post-Tonsillectomized Individuals, *Laryngoscope* **31** 310, 1929.

35 Ingersoll E. S. Surgical Study of 8,000 Tonsillectomies in Children. *Tr. Sect. Laryng., Otol. & Rhin., A. M. A.*, 1926, p. 142.

36 Paton, J. H. P. Tonsil-Adenoid Operation and Some of Its Results, *Quart. J. Med.* **22** 107, 1928.

before the age of 10 years is interesting and indicates that removal of the tonsils is not an effective means of avoiding otitis media

Neither the literature on the relation of otitis media to the condition of the tonsils nor the results of the present study furnish conclusive proof of the existence of a causal relationship between the tonsils and infections of the ear

RELATION TO RHEUMATISM AND ARTHRITIS

The literature on the relation of the condition of the tonsils to rheumatism and arthritis is so voluminous as to be impossible of citation. Only outstanding contributions, reports of research councils, a few observations of investigators in foreign countries and the recent literature can be reviewed.

The majority of textbooks both those dealing with conditions of the nose and throat and those dealing with general medicine emphasize the association of tonsillitis and diseases of the joints, and many advocate tonsillectomy as a cure or prophylaxis for arthritis and acute rheumatic fever. Some are emphatic in their attitudes, e. g., Tilly,³⁷ who included rheumatism and articular inflammations as indications for tonsillectomy, concluded by saying "It is reasonable to believe that the functions of the tonsils are of little importance, while their possibilities for evil when the balance between protection and invasion has been overcome are scarcely capable of exaggeration."

James Harper,³⁸ surgeon of diseases of the nose, throat and ear at the Royal Infirmary, Glasgow, after discussing possible functions of the tonsils, defended the practice of removing them "should there be any reason to suspect them of having an ill effect on the well being of the individual", he considered rheumatism as a definite indication for the operation. Kaiser¹⁰ gave the presence of positive or suspected evidence of the rheumatic syndrome—rheumatism, chorea, heart disease—as a definite indication for tonsillectomy, in view of the lessened incidence of heart disease in the group operated on. In a second article¹¹ however, in which he reviewed the histories and observations on 1,200 children presenting all or part of the rheumatic syndrome, among the 48,000 children included in the total survey, he said "Rheumatic fever, joint pain or growing pains occurred in both groups, 8 per cent in the tonsillectomized group, and 10 per cent in the nontonsillectomized group. Many of the former had had rheumatic symptoms before tonsillectomy. The tonsillectomized child not yet infected has a decidedly better chance to escape rheumatic infection over the same period of time than the child

37 Tilly, Herbert. *Diseases of the Nose and Throat*, ed. 4, London, H. K. Lewis & Company, 1919, p. 400.

38 Harper, James. *The Tonsil and Its Function*, Glasgow M. J. 94:344, 1920.

whose tonsils have not yet been removed. Recurrent attacks of rheumatic fever were less common in the groups in which operations had been performed."

Findlay, Macfarlane and Stevenson³⁹ thought that in the case of rheumatic manifestations characterized by arthritis the evidence in favor of the beneficial effect of tonsillectomy is slight. Robey⁴⁰ advocated removal of the tonsils during the active stage of rheumatic fever. The earlier the focus is discovered and removed, the more hope one has of lessening recurrences and the danger of cardiac involvement. In several cases in which symptoms recurred repeatedly he considered that the results of operation had been brilliant. Bertoin,⁴¹ of France, considered that extirpation is indicated in recurring inflammatory rheumatism if other sources of infection cannot be determined. When done in time, it may prevent serious diseases of the organism. After the appearance of these diseases, however, tonsillectomy is of no benefit and therefore, is not indicated. Wein,⁴² of Hungary, drew the following conclusion from 2,500 extirpations. Polyarthritis, acute glomerular nephritis and incipient endocarditis are frequently influenced favorably by tonsillectomy. Key-Aberg,⁴³ of Sweden, advocated that in every case, or at least in every recidivous case, in which practical experience has taught that the complaint may have originated in the tonsils, such as diseases of the kidneys and inflammatory rheumatism, the tonsils should be removed. The absence of visible pathologic changes of the tonsils does not offer a definite contraindication, considering the vital and social dangers of the diseases. Wodak,⁴⁴ of Czechoslovakia, included under strict indications for tonsillectomy, inflammatory rheumatism, other rheumatic processes, endocarditis and nephritis occurring one or more times after angina, so that their connection with the tonsils is established. Rosselli,⁴⁵ of Italy, favored the total removal of tonsils for the generally known and acknowledged indications

39 Findlay, L., Macfarlane, J. W., and Stevenson, M. M. Tonsillectomy in Prevention and Treatment of Rheumatism, *Arch. Dis. Childhood* **4** 313, 1929.

40 Robey, W., and Finland, M. The Effect of Tonsillectomy on the Acute Attack of Rheumatic Fever, Preliminary Report, *Arch. Int. Med.* **45** 772 (May) 1930.

41 Bertoin, Roger. Indications du traitement amygdalien dans le rhumatisme, *Zentralbl. f. Hals-, Nasen- u. Ohrenh.* **8** 335, 1925-1926.

42 Wein, Zoltan. Der gegenwartige Stand der Frage der Mandeloperationen, *Zentralbl. f. Hals-, Nasen- u. Ohrenh.* **8** 727, 1925-1926.

43 Key-Aberg, Hans. Ueber Tonsillektomie, besonders bei Kindern, *Zentralbl. f. Hals-, Nasen- u. Ohrenh.* **10** 841, 1927.

44 Wodak, E. Einige Bemerkungen uber Tonsillektomie, *Med. Klin.* **24** 807 (May 25) 1928.

45 Rosselli, Samvenero. La tonsillectomania totale. Indicazioni e tecnica, *Zentralbl. f. Hals-, Nasen- u. Ohrenh.* **12** 462 1928.

chronic tonsillitis, neoplasms, nephropathy, endocarditis, cryptogenic fevers and chronic rheumatism following angina. He argued that, whatever their function, it must fulfil its purpose in early youth and decrease with advancing age, and that the immediate and later dangers of the causes leading to tonsillectomy counterbalance the hypothetical damage done by the cessation of the function of the tonsils. Schneyer,⁴⁶ of Vienna, recommended tonsillectomy for acute rheumatism, polyarthritis and secondary chronic polyarthritis as a result of the first named disease. In the primary chronic arthritides there seems to be no causal nexus with infection of the tonsils, while in definite neuralgias and myalgias, tonsillectomy occasionally is of benefit.

Coombs,⁴⁷ of Bristol, England, considered that the finding of germs in the pericardial sac, subcutaneous nodules, cerebrospinal fluid, etc., is sufficient evidence of the fact that rheumatism is associated with an actual bacteremia. He thought the evidence for and against tonsillectomy hard to appraise, he operated only when there was an associated adenitis, or when removal of the tonsils was indicated because of their size, even apart from the coexistence of rheumatic infections. More than once he saw a severe recrudescence of the infection follow the excision of tonsils that had recently been the seat of an acute inflammation. Miller,⁴⁸ reporting in 1926 for a Subcommittee of the Science Committee of the British Medical Association on Rheumatic Heart Disease in Children said: "The effect of tonsillectomy on the rheumatic infections of childhood has up to the present, been mainly investigated by a follow up method. The results thus obtained have, as yet, proved very contradictory, and no judgment on the effect of the operations can be formed on them." He suggested as a "method of investigation which is far more applicable to the problem, the close study of the rheumatic infection as it occurs in children whose tonsils have been completely removed." Pemberton⁴⁹ studied 400 cases in soldiers. He considered the removal of foci of infection not always successful in relieving arthritis and not always the prime indication. When considered a contributing factor and remembered as that only, and not as a cure in itself, the operation is justifiable. Poynton⁵⁰ in the 1928

46 Schneyer, J. Zur Frage der Indikationsstellung zur Tonsillektomie bei Gelenk und sogenannten rheumatischen Erkrankungen, *Zentralbl f Hals-, Nasen- u Ohrenh* **13** 592, 1928-1929.

47 Coombs, C F. The Diagnosis and Treatment of Rheumatic Heart Disease in Its Early Stages, *Brit M J* **1** 227 (Feb 8) 1930.

48 Miller, R. Report on the Effect of Tonsillectomy on Rheumatic Infection in Children, *Brit M J* **2** 16 (July 3) 1926.

49 Pemberton, R. The Nature of the Influence of Focal Infection and the Means Necessary to Meet It, *Tr Am Laryng A* **33** 142 1923.

50 Poynton F J. Rheumatic Heart Disease in Childhood. *Tr M Soc London* 1928 p 313.

Lettsomian Lectures before the Medical Society of London, stated that he thought that there should be some collective studies of cases of rheumatism in children without tonsils. "If this proves to be frequent it must influence our procedure and make us tend to be cautious. Personally, I do not think that there is any more practical problem in the prophylactic treatment of rheumatic heart disease that requires more immediate attention, than does the correct line to take with the tonsils, for routine operation requires complete justification." Collins¹ said "The incidence of certain non-respiratory diseases varies with the condition of the tonsil. The incidence of illness from rheumatism, heart conditions, cervical adenitis, and ear conditions tends to be lowest among children with normal tonsils, higher among those with defective tonsils, and highest of all among those with removed tonsils. Presumably, these more or less chronic conditions clear up only slowly, if ever, after the tonsils have been removed. For this type of condition, special treatment in addition to the removal of tonsils may be necessary." Hajek⁵¹ felt that up to 1925 there had been no satisfactory statistics on the effects of tonsillectomy, and that results from diagnosis by elimination are unreliable. He pointed out the fact that physicians are of two opinions. 1. As far as diseases following tonsillitis—rheumatism, endocarditis, etc.—are concerned, the tonsils should not be considered as the primary site of the infection, then infection is simply a simultaneous manifestation of a septic infection at some other site. If one accepts this view, there is no justification for the removal of the tonsils, as the infection does not proceed from there. 2. The tonsils are primarily at fault, since numerous autopsies have shown the great probability that the tonsils are the primary entrance gates of infection and microscopic examinations have shown severe injury to the tonsillar tissue. Furthermore, experience proves that it is often possible to ameliorate or inhibit long-standing rheumatic infections by tonsillectomy.

Mygind⁵² connected tonsillitis with rheumatism, since patients as a rule suffer from a latent chronic angina long before a rheumatic fever develops. He stated that tonsils are not always necessary to rheumatic fever since patients without tonsils may contract the disease. Lindberg,⁵³ of Sweden, spoke from the point of view of a children's physician when he said that tonsillectomy rarely seems to benefit children. It is not indicated in rheumatic infections, should not be undertaken from a prophylactic standpoint and does not prevent relapses. Hajek,⁵¹

51 Hajek M. Die Tonsillektomie, Wien med Wchnschr **74** 17, 1924

52 Mygind, S. H. Quelques observations sur les rapports entre la tonsillite et les infections dites rhumatismales aiguës et la néphrite hémorragique aiguë, Acta oto-laryng **6** 335, 1924

53 Lindberg, Gustaf. Ueber Eingriffe an den Tonsillen vom Standpunkt des Kinderarztes Zentralbl f Hals- Nasen- u Ohrenh **11** 752, 1927-1928

of Vienna, thought the success of tonsillectomy for relative indications, in which he included rheumatism, endocarditis and nephritis, always doubtful. Hutter,⁵⁴ of Vienna, thought that it would by all means be a mistake to recommend tonsillectomy in all cases of rheumatism, because the question of whether acute or chronic recidivous polyarthritis is or is not always due to the tonsils needs a great deal of further study. Schoen,⁵⁵ of Germany, followed 100 cases in which tonsils were removed for diseases of the joints, endocarditis or nephritis, and found a cure of acute rheumatism seldom accomplished. He thought that the operation had some effect in preventing relapses. Jarlov and Kragh,⁵⁶ of Denmark, discussed 89 cases of rheumatic infection and concluded "Tonsillectomy cannot be credited with any appreciable influence on the cure or amelioration of rheumatic diseases of the joints."

Campbell and Warner⁵⁷ contrasted groups of children at Guy's Hospital, 843 with, and 124 without tonsils, and found 15.3 per cent of the former and 15.6 per cent of the latter to have rheumatism. They said that many enthusiasts claim that tonsillectomy would have prevented the first manifestations of rheumatism, but that their statistics do not support this view. They found no evidence that the tonsils of rheumatic children are more septic than those of nonrheumatic children attending the outpatient clinic. The frequency of tonsillitis, the septic appearance of the tonsils and the degree of enlargement of the lymph glands are similar in the two groups. Moreover, complete enucleation of the tonsils before there were any signs or symptoms of rheumatism (on an average, two years before) did not prevent its onset, diminish its frequency or in any way lessen the incidence of rheumatic carditis. Thus there is no evidence to support the theory that tonsillectomy should be performed as a routine measure at an early age to prevent rheumatism.

Boas and Schwartz⁵⁸ said "In spite of our increasing knowledge of rheumatic fever, there is a persistent tendency to focus attention too exclusively on the heart and too little on the systemic infection. It is true that the enthusiasm for the eradication of foci of infection in the tonsils and teeth has led toward a broader concept of the nature of

54 Hutter, Fritz. Tonsillen und interne Erkrankungen, *Zentralbl f Hals-, Nasen- u Ohrenh* **12** 88, 1928.

55 Schoen, R. Erfahrungen über den Wert der Tonsillektomie bei internen Krankheiten, *Klin Wchnschr* **7** 2268, 1928.

56 Jarlov, E, and Kragh, J. Die Bedeutung der Tonsillektomie bei chronischen Gelenkerkrankungen, *Zentralbl f Hals-, Nasen- u Ohrenh* **12** 711, 1928.

57 Campbell, M, and Warner, E. C. Rheumatic Disease in Children, *Lancet* **1** 61 (Jan 11) 1930.

58 Boas, E. P, and Schwartz, S. P. Some Modes of Infection in Rheumatic Fever, *Am Heart J* **2** 375, 1927.

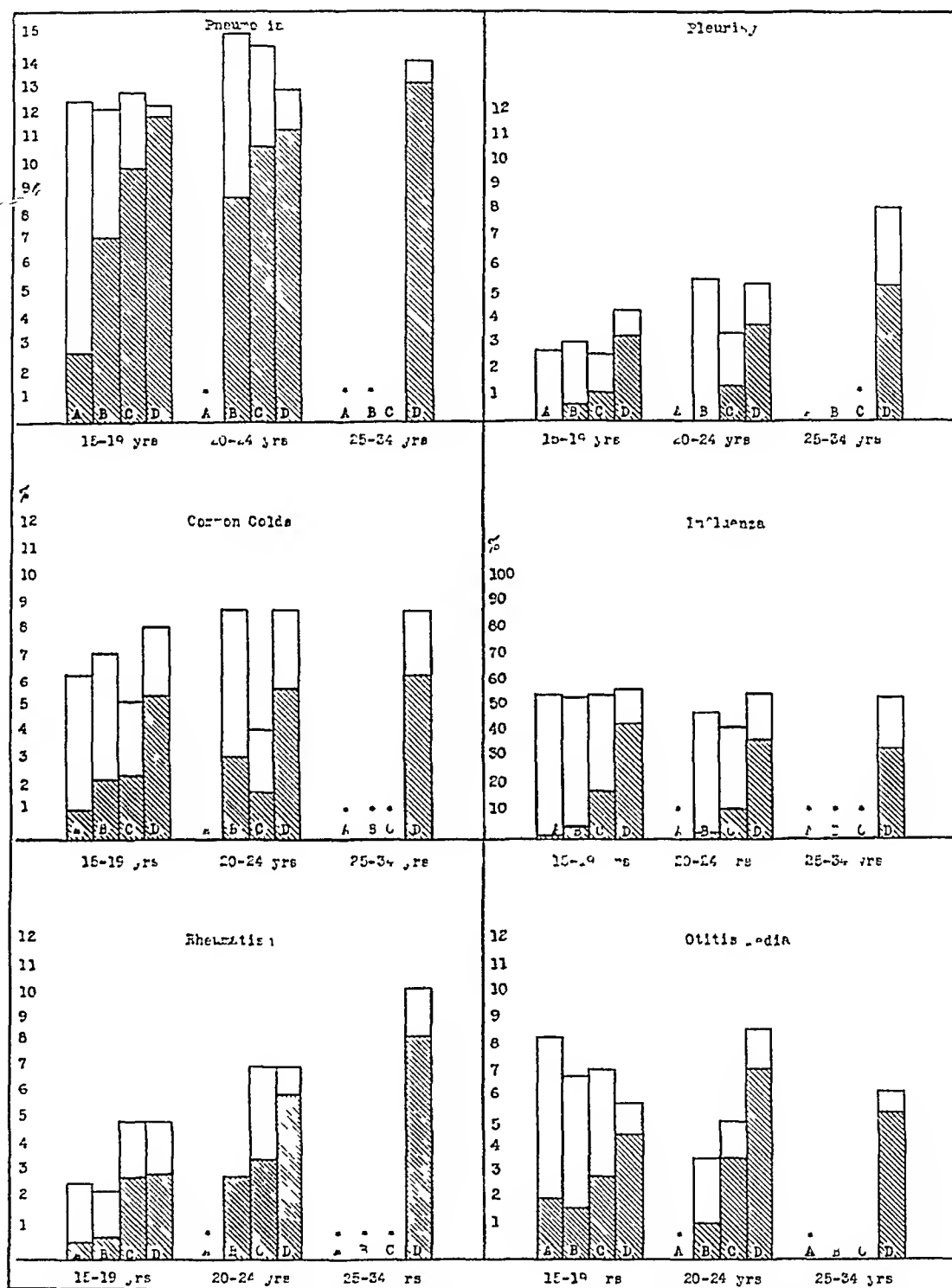


Chart 6—Incidence of infections of the respiratory tract, according to age and the year when the tonsils were removed

rheumatic heart disease but the results of these measures have been rather sterile in their benefit to the patients and to the progress of knowledge

Of what avail is tonsillectomy when the virus may persist in the heart, synovia, or subcutaneous nodule for months at a time, ready to give rise to infection?"

The history of rheumatism in the present study is inaccurate and probably includes many kinds of painful experiences toxic, infectious, metabolic and traumatic arthritides and myositides, as well as cases of acute articular rheumatism. The groups of persons with normal and pathologic tonsils had about equal experience with this type of pain, whereas those whose tonsils had been removed showed about twice the percentage of incidence (table 2 and chart 2). The percentage difference is not statistically significant between the groups of those with normal tonsils and those with pathologic tonsils, but is significant between the groups of those with normal tonsils and those with tonsils that have been removed (tables 3 and 4). Of all systemic infections rheumatism probably offers the chief indication for the removal of tonsils. It was found in the present study that a high proportion of persons whose tonsils had been removed had "rheumatism" before operation (tables 5, 6 and 7 and chart 6). Both in the 15 to 19 and in the 20 to 24 year groups, those whose tonsils were removed before 10 years of age suffered less than those whose tonsils were removed in later years. However, in the group from 15 to 19 years of age those whose tonsils were removed before 10 years of age had considerable "rheumatism" following tonsillectomy.

From the cases studied, the arguments as to the value of removing the tonsils as a prophylaxis for "rheumatism" do not seem conclusive. If tonsillectomy is of value here, its influence seems of minor rather than of major importance. The literature on the subject is extensive and varied in its arguments. In recent years there seems to be an increasing tendency to question the preventive or curative value of tonsillectomy for rheumatism.

RELATION TO CHOREA

Chorea has frequently been included in the group with tonsillitis, rheumatism and carditis, in which tonsillectomy was recommended as a prophylaxis and cure. Kaiser¹¹ found that chorea occurred only slightly less often following tonsillectomy in 0.4 per cent of 1,200 children without tonsils as compared with 0.5 per cent of the same number of children with tonsils. The incidence of carditis following chorea however, was decidedly less in the tonsillectomized children. Cummings³² listed chorea as an indication for removal of the tonsils. Farnum⁵⁹

⁵⁹ Farnum, W. B. Tonsillectomy. The Effect on Existing Cardiac Disease in Adults, *Am J M Sc* **176** 474 1928

studied 526 patients in a cardiac clinic before and after tonsillectomy, 51 per cent of whom had had chorea. He stated that in this group tonsillectomy did not seem to have a great effect on the recurrence of chorea, as about 20 per cent of cases recurred in both the tonsillectomized and the nontonsillectomized group. Clowe, Watkins and Rothholz⁶ did not find tonsillectomy satisfactory in curing patients who had chorea. In discussing Pratt's⁶⁰ paper, "The Results of Tonsil Operation," McCulloch said: "We have come to look at the tonsils as a focus of infection causing rheumatic fever, heart disease and chorea." Bailow, in continuing the discussion, pointed out "the tendency on the part of the physician to imply brilliant results where there is no ground for such an attitude." Findlay, Macfarlane and Stevenson³⁹ concluded that a preliminary tonsillectomy may render a person less susceptible to rheumatic arthritis, but not to chorea.

Although there was a history of much less chorea than of rheumatism among the young women entering the University, the relationship of the frequency of chorea in the three groups—those with normal, those with absent, and those with pathologic tonsils—was much the same as that of rheumatism (table 2 and chart 2). Those whose tonsils had been removed had about twice the percentage of chorea shown by those in the other two groups. Those with pathologic tonsils had had slightly more chorea than those with normal tonsils, which is not the case with rheumatism. Statistical value can be credited to differences in the percentage incidence of chorea in the group with normal tonsils and in the group of those whose tonsils have been removed, but not between the groups with normal tonsils and those with pathologic tonsils (tables 3 and 4).

RELATION TO DISEASES OF THE HEART

The increasing frequency of disease of the heart as a cause of death has focused attention on the etiology of cardiac pathology and on the methods of preventing damage to the heart.

Kaiser,⁶¹ from 1919 to 1921, surveyed 48,000 school children in Rochester, N. Y., and found rheumatic heart diseases in 450, or 22.2 per cent of the 20,000 who had had their tonsils removed, and in 817 or 29 per cent of the 28,000 who were not operated on. In many of the children in the former group heart disease developed before enucleation of the tonsils, since a careful analysis of 478 cases of carditis showed that the condition developed in 83 per cent before removal of the

60 Pratt, F. J. Results of Tonsil Operation. Questionnaire Report. *Arch Otolaryng* **4**: 142 (Aug.) 1926.

61 Kaiser, A. D. Relation of Tonsils to Acute Rheumatism. *Am J Dis Child* **37**: 559 (March) 1929.

tonsils and in 17 per cent following tonsillectomy Nobel and Hecht,⁶² reporting from the University Clinic in Vienna, stated that a relation between diseases of the tonsils and other organic diseases, such as rheumatism, endocarditis and nephritis, frequently exists, but that as a rule it cannot be diagnosed by an examination of the tonsil alone. A seminar of Viennese physicians,⁶³ meeting in 1928 to discuss the indications for removal of the tonsils, especially for general diseases, expressed the belief that the exacerbations of endocarditis and nephritis that frequently follow tonsillectomy speak for the tonsillogenic cause of the disease, they thought that, if possible, removal of the tonsils should not be undertaken until after the acute stage of the disease. Haardt⁶⁴ agreed with the Viennese group as to the time for removing tonsils, since in twenty-one patients operated on at an early stage, two showed symptoms of marked general infection, with elevation of temperature to 40 C (104 F). Schoen⁵⁵ found tonsillectomy important in inhibiting relapses of endocarditis. Farnum⁵⁹ studied 526 patients in a cardiac clinic. He stated that in adults with existing cardiac disease, the hope for improvement from tonsillectomy has been based on a shaky foundation. If tonsillectomy is to be generally used as a definite therapeutic measure in cardiac disease, its best results will be obtained before the incidence of cardiac infection or very early in its course. Rheumatic carditis in all its manifestations is but one phase of a generalized infection spoken of as rheumatic fever. Removal of the tonsils, although accomplished before carditis occurs, will not prevent its occurrence. The removal of the tonsils alone will not guarantee a halt in the progress of existing cardiac disease because the cause of the infection may still be present in the throat or elsewhere in the body. The preventive treatment should be based on raising the individual resistance to infection by all possible means.

In the histories and physical observations in this study, considerable attention was given to cardiac conditions, since placement in physical education classes in the university depends on the entrance examination. Evidence of damage to the mitral valve was less among those with normal tonsils than among those with absent or pathologic tonsils (table 11 and chart 7). The latter two groups seem to suffer equally. It may be that in a high percentage of cases hearts are permanently damaged by pathologic tonsils before tonsillectomy, or persons susceptible to

62 Nobel, E, and Hecht, A. F. Ueber die Tonsillenfrage, *Klin Wchnschr* 4 1049 (May 28) 1925

63 Seminar of Viennese Physicians. Wann sollen die Tonsillen entfernt werden und besonders bei welchen internen Krankheiten? *Wien klin Wchnschr* 41 867, 1928

64 Haardt, W. Zur Frage des Zeitpunktes der Tonsillektomie beim Peritonsillarabscess, *Zentralbl f Hals-, Nasen- u Ohrenh* 12 20, 1928

tonsillar disease are also susceptible to cardiac damage. The same agent that causes damage to tonsillar tissue may, without the relationship of cause and effect, cause damage to the heart. Lesions to the aortic valve, although few, seemed to indicate a protective effect of tonsillectomy, since the group whose tonsils had been removed showed

TABLE 11—*Condition of the Heart as Related to That of the Tonsils*

	Tonsils											
	Normal		Absent		Pathologic		Remnants		Buried or Projecting		Total	
	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent
Mitral damage	84	2.05	140	3.45	95	3.42	7	2.17	23	2.28	349	2.85
Aortic damage	22	0.54	10	0.25	23	0.83	1	0.31	5	0.50	61	0.50
History of cardiac disease	132	3.23	207	5.10	84	3.02	8	2.48	45	4.46	476	3.88
Total number in group	4,091		4,058		2,779		322		1,010		12,261	



Chart 7—Incidence of diseases of the heart. In this and chart 8 the black column indicates the group with normal tonsils, the next column those whose tonsils had been removed and the third column those with pathologic tonsils. Scale indicates per cent.

about one-half of the percentage of damage, as did those with tonsils judged as normal, and about one third the percentage of damage of those with pathologic tonsils. If all observations relative to the tonsils and cardiac conditions were of this pattern, the evidence in favor of tonsillectomy as a prophylaxis against cardiac disease would be clear. Although the diagrams and tables look convincing, no differences in percentages between the condition of the aortic valve in tonsil groups have statistical weight, and such differences as do occur must be taken as suggestive and not as final (tables 3 and 4). The history of cardiac disease, with or without accompanying physical observations, was approximately equal for the group with normal tonsils and that with pathologic tonsils, but considerably greater for the group with absent tonsils. Since the combined damage to the mitral and aortic valves in

the group with pathologic tonsils is not as much greater than that in the group with absent tonsils, as is the history of heart trouble in the group with absent tonsils greater than a similar history in the group with pathologic tonsils, some slight hint is offered of the curative action of tonsillectomy in early cardiac involvement

The same lack of conviction as to the relationship between the condition of the tonsils and rheumatism is found in both the literature and the results of the present study for the relationship between the tonsils and cardiac conditions. Here, also, recent investigators tend to question the previously accepted relationship of cause and effect

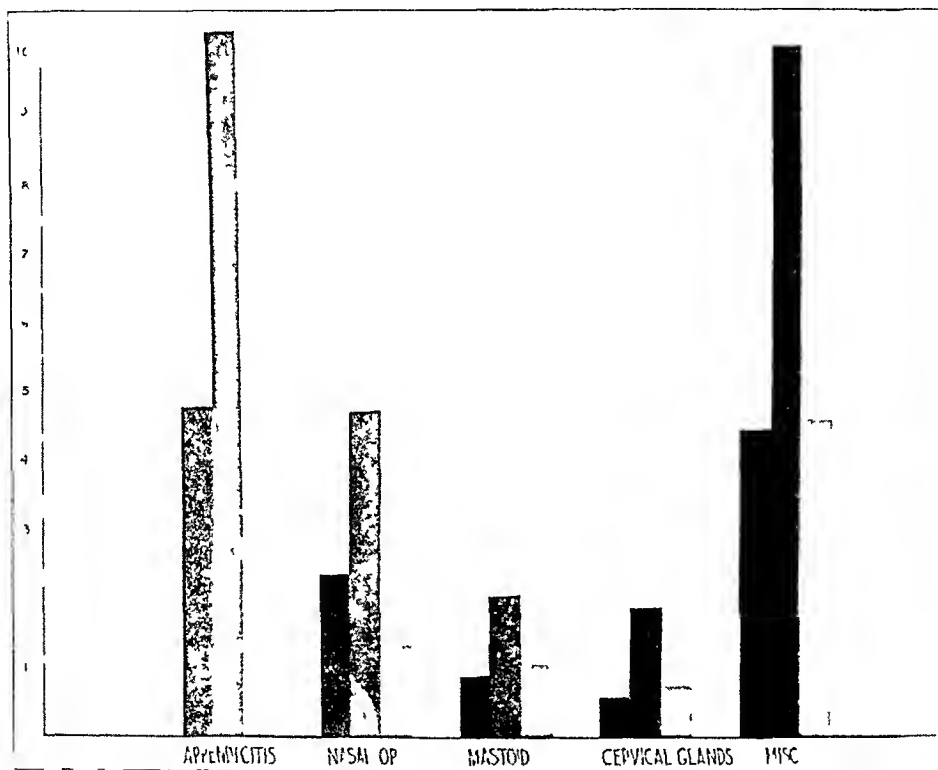


Chart 8—Incidence of operations, by groups. Scale indicates per cent

HISTORY OF OPERATIONS

Only the operations resulting from infectious processes and structural defects are considered (table 12 and chart 8). Those necessitated by mechanical defects, such as the plating or wiring of fractures, the removal of foreign bodies and the transplanting of tendons, are not included.

The correct interpretation of the observations on operations is probably impossible. The mental attitude toward medical care and operations in particular is apparent in that the groups accepting tonsillectomy accepted other operations in much greater numbers than did those with normal or pathologic tonsils. Even religious principle may

play a part here. It is possible that some persons with pathologic tonsils, refusing the advice to have their tonsils removed, also refused an appendectomy or delayed it too long and, through death, lessened the number of those entering the university with pathologic tonsils and with a history of appendectomy. This cannot, however, account for the entire difference between the greater number of those with normal tonsils and a history of appendicitis than those with pathologic tonsils and a similar history (table 12 and chart 8). In the group with pathologic tonsils many acute abdominal pains may have subsided undiagnosed, without operation, and their sufferers survived more by good luck than by good management. Considering the history of appendicitis without operation, it is apparent that all persons whose ton-

TABLE 12—*The Incidence of Operation, According to the Condition of the Tonsils*

	Tonsils											
	Normal		Absent		Pathologic		Remnants		Buried or Projecting		Total	
	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent
	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent
Appendectomy	198	4.73	419	10.14	127	4.48	24	7.29	55	5.26	823	6.57
Operation on glands of neck	24	0.57	74	1.79	28	0.99	3	0.91	9	0.86	138	1.10
Nasal operation	85	2.03	193	4.67	35	1.23	12	3.65	17	1.62	342	2.73
Mastoid operation	32	0.76	81	1.96	20	0.72	3	0.91	7	0.67	143	1.14
Total number in group	4,185		4,134		2,836		329		1,046		12,530	

sils had been removed were not operated on when a diagnosis of appendicitis was made. Over 3 per cent of those in the group with normal tonsils and of those in the group with pathologic tonsils gave a history of appendicitis without operation, whereas over 6 per cent of the group whose tonsils had been removed gave a similar history (table 2).

SUMMARY

1 The histories of young women entering the University of California during the last ten years were transferred to punch cards.

2 Of these cards, 12,530, representing white women of from 15 to 34 years of age, were sorted and tabulated as to the condition of the tonsils and as to the incidence of illnesses and operations in the three groups, the results showed 4,185 with normal tonsils, 4,134 with absent tonsils and 2,836 with pathologic tonsils.

3 The inaccuracies of the histories, observations and method were considered.

4 Tables and diagrams of the incidence of disease and operation, with standard errors of differences in percentages in the groups are presented

5 The cards were sorted according to age groups, from 15 to 19, from 20 to 24 and from 25 to 34 years, and according to the condition of the tonsils for the history of disease and of operation

6 The cards of the group with absent tonsils were sorted, by age groups, to indicate whether the disease or operation preceded or followed the tonsillectomy

7 The cards of those without tonsils were sorted according to (1) age groups, (2) the age when the tonsils were removed, from 0 to 4, from 5 to 9, from 10 to 14, and 15 years and over, and (3) for facts in the history

8 Tables and diagrams present the observations made in this study

9 Facts not discussed in the text are included in the diagrams and tables in the hope that they may serve as source material

10 The literature concerning the relation of the condition of the tonsils to the incidence of measles, mumps, chickenpox, whooping cough, scarlet fever, diphtheria, infections of the upper respiratory tract (influenza not included), tonsillitis, otitis media, rheumatism, chorea and cardiac conditions has been partially reviewed

CONCLUSIONS

1 One third of 12,530 young white women who entered the University of California between 1920 and 1929 had had an operation for the removal of tonsils, one-third were thought to have normal tonsils, and the remaining one-third had pathologic tonsils, remnants of tonsils or buried or projecting tonsils to which no further designation was given

2 The group with normal tonsils and the group with pathologic tonsils differ by small percentages, which are statistically insignificant in the incidence of the following diseases and operations reported in the histories: measles, mumps, chickenpox, whooping cough, scarlet fever, diphtheria, pneumonia, pleurisy, chronic colds, rheumatism, chorea, operations for appendicitis, mastoiditis, cervical glands and operations on the nose

3 The group with absent tonsils gave a history of higher incidence of all illnesses and operations than did either the group with normal tonsils or the group with pathologic tonsils. The fact that children who are often ill are the ones most frequently operated on is offered as a possible explanation for this higher incidence of illness

4 The proportion of the amount of illness reported before and after tonsillectomy suggests that the removal of tonsils had little influence in lessening the susceptibility to most infections. The lack of proper comparative data lessens the value of this conclusion.

5 The age when the tonsils were removed had no influence on the total incidence of measles, mumps, chickenpox, whooping cough, pneumonia and influenza, but early removal seemed to have a slightly favorable influence on the incidence of scarlet fever and, to a less extent, on that of diphtheria. The effect of the age of removal on chronic colds, rheumatism and otitis media was not conclusive.

6 A review of the literature relative to the effect of the condition of the tonsils on general health reveals a great lack of accurate information on the effect of tonsillectomy, when one considers the number of operations that have been performed. Opinions as to the indications for, and the value of, tonsillectomy vary widely. There is a growing tendency to question the value of tonsillectomy as a prophylaxis against infectious diseases and as a preventive measure or cure for such systemic diseases as rheumatism, chorea and carditis.

CHRONIC ENDEMIC ERGOTISM

ITS RELATION TO THE VASOMOTOR AND TROPHIC DISEASES¹

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Epidemic ergotism has practically been extinct since the end of the last century. The more careful cleaning of the rye seed before planting and milling undoubtedly accounts for the great reduction of the torturing pains and mutilations that resulted from the eating of rye bread infected with ergot. Our economic system, through which grains are stored for long periods, is another important element in preventing ergotism. It is well known that the toxicity of ergot decreases with age. During the epidemics it was noticed that ergot was most harmful soon after the harvest, that the toxicity decreased considerably toward spring, and that by summer the ergot was practically harmless.

If it were not for the careful cleaning and long storing of the grain, conditions similar to those that occurred during the epidemics might be witnessed, as even today many rye fields are heavily infected with ergot. Atanasoff¹ said:

Grains, especially rye, in some seasons and in some fields are infected so heavily that every head may have one or more sclerotia, as was reported from Wisconsin in 1917.

Cases where 20 to 50 per cent of the heads were infected with ergot have been reported from various parts of the United States and Europe.

The amount of ergot for 1917 in Connecticut ranged from one to five per cent. Decrease of the yield (of rye) by as high as 20 per cent has been reported from Russia (as a result of ergot infection).

Ergot has been found in every continent on the globe. It attacks all the grains and grasses, but rye is its principal host. In North America it has been found in Vermont, Connecticut, New York, Michigan, Tennessee, Indiana, Wisconsin, Minnesota, Iowa, Kansas, Wyoming, Montana and other states besides various localities in Canada.

The importance of the present day infection can be judged by the defensive measures of the farmers and millers to remove the fungus. Many methods, such as sifting, screening and sedimentation, are employed, which Atanasoff said may reduce the amount of ergot to from 0.06 to 0.17 per cent. It is, of course, not expected that such

¹ Submitted for publication, Sept. 2, 1930.

From the Pathological Department of the Sydenham Hospital.

¹ Atanasoff, D. Ergot of Grains and Grasses, Monograph, U. S. Dept. Agric., Washington, 1920.

a reduction could occur where the infection with ergot was very heavy. I have examined many samples of rye flour from various regions, and have found few that were not contaminated with ergot, some of them contained a considerable quantity.

A study of the literature of epidemic ergotism and my experimental investigations of ergotism in fowl have suggested to me the possibility that the cause of some of the vasomotor and trophic diseases can be traced to endemic ergotism. Of course, it would be impossible to prove this until more facts have been obtained. However, I believe that there is sufficient evidence in the form of pathologic analogies and the widespread consumption of ergot to make this fungus the subject of greater study in relation to such diseases as thrombo-angitis obliterans, Raynaud's disease, erythromelalgia, acio-asphyxia, scleroderma, sclerodactylia, multiple neurotic gangrene, dermatomyositis and other such diseases of unknown origin. The relationship between ergotism and this group of diseases was hinted at in an article in which I attempted to show the similarity of thrombo-angitis obliterans and ergotism (gangrenous form). Much of the details in the etiology, pathology, toxicology and symptomatology of these two conditions, which are omitted here, will be found in that article.²

Considering the amount of rye infected with ergot that is consumed here and abroad, it is surprising that cases of endemic ergotism are so rarely reported.³ It may well be that chronic endemic ergotism occurs in the guise of the vascular, vasomotor and trophic diseases mentioned. These sequelae to ergot poisoning are perhaps overlooked because of the mildness of the original intoxication and the insidious onset of the later manifestations.

That Raynaud⁴ suspected ergot to be the cause of the disease named after him is borne out by his experimental attempts to produce this

2 Kaunitz, Julius. The Pathological Similarity of Thrombo-Angitis Obliterans and Endemic Ergotism, *Am J Path* 6 299-315 (May) 1930.

3 Since writing this, I have come across the article of Robertson and Ashby (Ergot Poisoning Among Rye Bread Consumers, *Brit M J* 1 302, 1928) and Morgan (Report on an Outbreak of Alleged Ergot Poisoning by Rye Bread in Manchester, *J Hyg* 24 51, 1929) of a small outbreak of acute ergotism occurring in Manchester as late as 1928. It affected only the members of the Jewish population who ate rye bread. The rye flour contained approximately 1 per cent ergot, which appeared to be harmful only soon after the harvest, when it was fresh. The vasomotor and trophic symptoms were milder than those mentioned of the epidemics. Improvement was observed in some cases when the use of rye bread was discontinued.

4 Raynaud, Maurice. On Local Asphyxia and Symmetrical Gangrene of the Extremities, *Trans by Thomas Barlow, Selected Monographs*, London: New Sydenham Society, 1888, p 130.

disease in animals Ehlers⁵ not only suspected Raynaud's disease but also erythromelalgia, acrodynia and other vasomotor disturbances as being due to ergot

SUSCEPTIBILITY

General Considerations—The Abbe Tessier⁶ formed a good judgment of the conditions likely to promote an outbreak of ergotism (he speaks of La Sologne)

these are three 1 That the district was damp and foggy, 2 that the vegetable products were ill-thriven and stunted, 3 that the inhabitants were in bad health, being reduced by want and malaria

It was noticed that those persons whose diet also contained milk, cheese or meat in addition to rye bread suffered less severely or not at all The rôle played by a diet almost exclusively of rye bread or the addition to it of dairy foods and meats deserves consideration These animal foods may serve as a protection against ergotism in the same way as they do against pellagra, another grain disease

The increased susceptibility brought about by starvation, misery and ill health mentioned by Tessier is true of many other diseases

Sex and Age—In a survey of sixty-eight epidemics, Krynsky⁷ found that with one exception the gangrenous form of ergotism affected the males exclusively The convulsive form affected the women, children and the aged Tessier⁸ observed that the spurred rye acts with less force on females Renaudin⁹ stated that the gangrenous form of ergotism does not affect females Noel,¹⁰ surgeon of the Hotel Dieu of Orleans, describing an epidemic of 1710, said of ergot " attacks men by preference what is most astonishing, does not attack women " What is true of epidemic is also true of medicinal ergotism In spite of the tremendous quantity of ergot administered to women in this country—from 170,000 to 264,000 pounds

5 Ehlers, Edvard *Ignis sacer et Sancti Antoni*, Kjøbenhavn, Ernst Bojesen 1895, pp 68-79

6 Tessier, Abbe *Recherches sur le feu Saint Antoine*, par Jussieu, Raulet, Sailant, Tessier, etc, *Hist Acad roy d sc*, 1776, quoted from Ailbutt and Rolleston *System of Medicine*, New York, The Macmillan Company, 1906, vol 2, part 1, p 886

7 Krynsky, Stanislaus *Pathologische und kritische Beiträge zur Mutterkornfrage*, Monograph, Jena, Gustav Fischer, 1888

8 Tessier, Abbe *Traite des maladies des grames*, Paris, 1783, 8 vols, quoted by Neale, Adam *Spur or Ergot of Rye*, London, H Phillips, 1828, vol 8, p 18

9 Renaudin *Dictionnaire des sciences medicales, ergotisme*, Paris, 1815 vol 8, quoted by Neale, Adam *Spur or Ergot of Rye*, London, H Phillips, 1828, vol 8, p 18

10 Noel, quoted from Raynaud (footnote 4, p 131)

(77,100 to 119,700 Kg) imported yearly ¹¹—one rarely hears of a case of gangrene in women from this source

When the eye is heavily infected with ergot, as during epidemics, because of the overwhelming quantity few persons escape its mutilating effects. However, when the infection is slight, only those persons who are most susceptible suffer from its effects, the intoxication being more selective and, on account of the different individual idiosyncrasies, assuming different forms of vascular, vasomotor or trophic manifestations

One of the severest vascular conditions in this study is found in thrombo-angitis obliterans. This disease occurs most frequently in young and middle-aged men, but is rare in women. Raynaud's disease, however, occurs more frequently in women. Ergotism, as we have mentioned, also produces gangrene in young and middle-aged males, but rarely in females. It is pertinent to consider here the possibility that men who are most susceptible to ergot are more frequently affected with the severer pathologic condition of thrombo-angitis, while the women, who are less susceptible, are more frequently affected with a milder condition of Raynaud's disease

SYMPTOMATOLOGY

The different symptoms and signs that occur in Raynaud's disease, such as erythromelalgia, sclerodactylia, scleroderma, etc., are well known. It is because of the distinctions in these symptoms and signs that the classification is made. It frequently happens, however, that the symptoms of two or more of these conditions are found associated. Raynaud's disease, for instance, may exhibit symptoms of erythromelalgia, sclerodactylia or scleroderma. Scleroderma frequently is found associated with sclerodactylia. It is not unusual to find symptoms and signs of the vasomotor and trophic group of diseases, especially Raynaud's disease, erythromelalgia, scleroderma, sclerodactylia, etc., associated with thrombo-angitis obliterans. The frequent association of these various syndromes must be considered as something more than a coincidence

In epidemic ergotism, all of the vasomotor disturbances were noted. Pallor, rubor and cyanosis were frequently accompanied by excruciating pains of a burning or clamping nature. Paresthesias, such as formication, heat, coldness and anesthesia were some of the other sensory disturbances noted. Trophic changes, such as ulceration, desquamation, shriveling or withering of the tissues or whole extremities were some of the sequelae. The pulse was found to tighten from day to day and

11 Department of Commerce of the United States, private communication

finally to become obliterated. Cyanosis gave way to blackness, which was followed by gangrene, generally of a dry nature, in the fingers, toes, hands or feet, the entire extremity or in patches over the trunk, extremities, ears, nose or viscera. These symptoms were generally more acute than those in the group of diseases under consideration. To my knowledge, the chronic cases of ergotism that might belong to this group were not chronicled during the epidemics. They might have passed then, as they do today, for different conditions. Today, with no definite human ergotism as a basis, it is even more difficult to appraise the causal relationship of ergot. In cases of thrombo-angitis obliterans, I was able to collect considerable evidence of the disease occurring in those who eat rye bread.

The symptoms of the vasomotor and trophic diseases that are being considered may be found in various combinations of those found in ergotism, the following of which are a few brief examples.

In thrombo-angitis obliterans, one may find all the vasomotor disturbances manifested by pallor, rubor and cyanosis, and sensory disturbances of severe burning or clamping nature, paresthesias such as formication, coldness, heat and anesthesia. Local edema or atrophy with trophic ulcers generally occurs in the toes and fingers. These symptoms may precede or occur simultaneously with the obliteration of the pulse in an extremity. The terminal infarction usually occurs in the extremities and occasionally in the viscera, the symptoms of the latter condition resembling those of colonic, mesenteric and other visceral thromboses.

In Raynaud's disease, pallor, rubor and cyanosis may occur paroxysmally and bilaterally, in the extremities, in the tip of the nose or ears, or in patches over the body as in multiple neurotic gangrene. Local edema or atrophy with trophic ulcers and severe pain, paresthesias and anesthetics are some of the other manifestations in the affected regions. The pulse may be obliterated during the arterial spasm. Persistent cyanosis is followed by blackness and finally gangrene in the affected regions. Epileptic seizures, paroxysmal hemoglobinuria and other visceral conditions have been attributed to this condition. The distribution of Raynaud's disease is much like that of epidemic ergotism.

In erythromelalgia the vasomotor symptom is generally rubor, which is followed by cyanosis in the part of the extremity affected. Excruciating burning pains are experienced, particularly when the extremity is in the pendant position. Edema and trophic disturbances and ultimately gangrene usually follow the vasomotor phenomena. The distribution is practically limited to the hands and feet.

Chronic acro-asphyxia generally exhibits a cyanosis which, though of a chronic nature, may occasionally be paroxysmal in its attacks. Pain

is usually absent, there being instead a hypoaesthesia, coldness and numbness. Edema and trophic ulcers are generally found in this condition, the distribution is practically limited to the hands and feet.

Scleroderma frequently begins with the vasomotor symptoms of Raynaud's disease. The skin is either blanched, hyperemic or cyanotic. The hand edema is followed by induration which may occur in patches or all over the body. Sensory disturbances of burning pains, formication and numbness are complained of. Trophic ulcers and gangrene, particularly the former, are commonly encountered. When sclerodactylia is an associated complication, atrophy or withering of the fingers takes place, the terminal phalanges becoming absorbed.

In dermatomyositis, as in scleroderma, the skin is said to exhibit vasomotor disturbances which are followed by edema and later induration. In some cases the muscles are markedly inflamed and excruciatingly painful, particularly on motion. This rare disease is only mentioned because of some suggestive pathologic observations connected with it that I obtained in experimental ergotism.

ONSET AND COURSE

During the epidemics, ergotism frequently ran an acute course. Starting with shock, gastro-intestinal and nervous symptoms, death followed as after severe intoxication. In the more chronic form, the intoxication usually manifested itself immediately and occasionally many months after exposure to cold or an acute infectious disease, when gangrene of the extremities or infarction of the viscera would ensue. During the epidemics, it was also noticed that after the amputation of one of the gangrenous limbs, the symptoms receded or disappeared until some future epidemic when gangrene of another limb became evident. The epidemics are too far removed for one to decide whether the succeeding attacks were due to the original intoxication with ergot and not to the later epidemic. There is a certain amount of evidence supporting the idea of an immunity to ergot which results from previous inoculation or ingestion of ergot. If this is true, one must consider that the secondary attacks of gangrene were not so much the result of the reingestion of ergot, but were due to the vascular lesions that the previous intoxication had caused. In horses whose hooves or tails sloughed off after intoxication with ergot, Buffum¹² noticed that gangrene was occasionally delayed two years after the original intoxication. In thrombo-angitis obliterans, one limb after another becomes involved, until in some cases amputation has been

¹² Buffum, B. C. Grasses and Forage Plants, Wyoming Agric. Exper. Sta. Bull. 16 223-248, 1893, quoted by Atanasoff (footnote 1)

performed on both upper and lower extremities. Occasionally, in a milder form, the same sequence has been observed in Raynaud's disease. The co-existence of endarterial lesions in apparently healthy extremities in cases of thrombo-angitis obliterans has been demonstrated. One frequently finds many stages of this vascular disease present. It appears suggestive that as a result of earlier intoxication vascular changes are

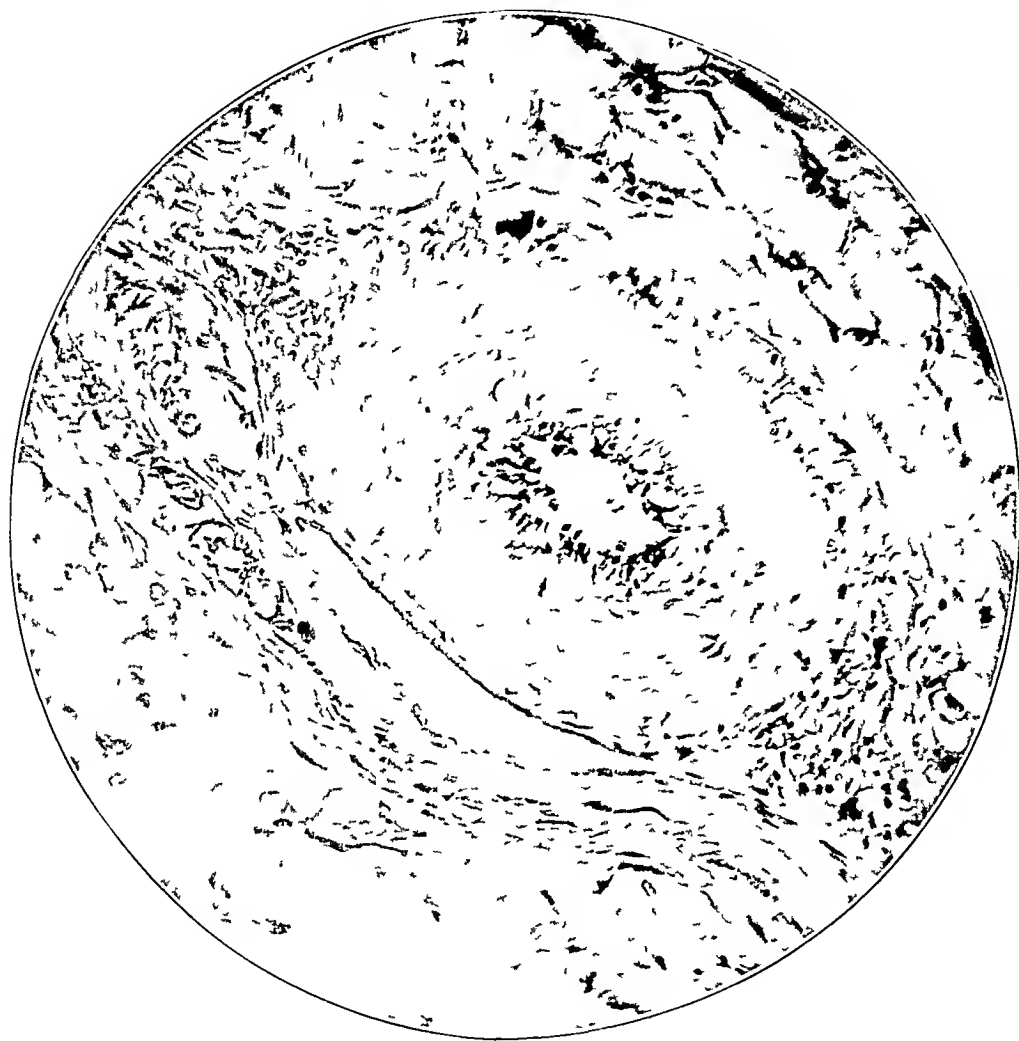


Fig 1—Acute ergotism. Photomicrograph of the artery of the median stalk at the base of the cock's comb. The media appears thickened and edematous. The nuclei stain poorly, suggesting attrition due to continual angiospasm. The lumen of the vessel, which is considerably narrowed, was perhaps more contracted during life. The pathologic sequelae in these vessels can only be surmised by the lesions found in figures 4 and 5, which show chronic manifestations.

provoked, particularly in the extremities. The change in the peripheral tissues results from the organic and functional interference with the circulation in these tissues. An acute onset following an acute infectious disease is frequently met with in Raynaud's disease and in erythromelal-

gia and is comparable to the manifestations of ergotism that are provoked by an acute disease long after the intoxication with ergot. In most of the diseases of this group, there is a chronic course.

PATHOLOGY

The intrinsic pathologic processes in these vascular and trophic diseases that have been considered is anything but an open book. Of

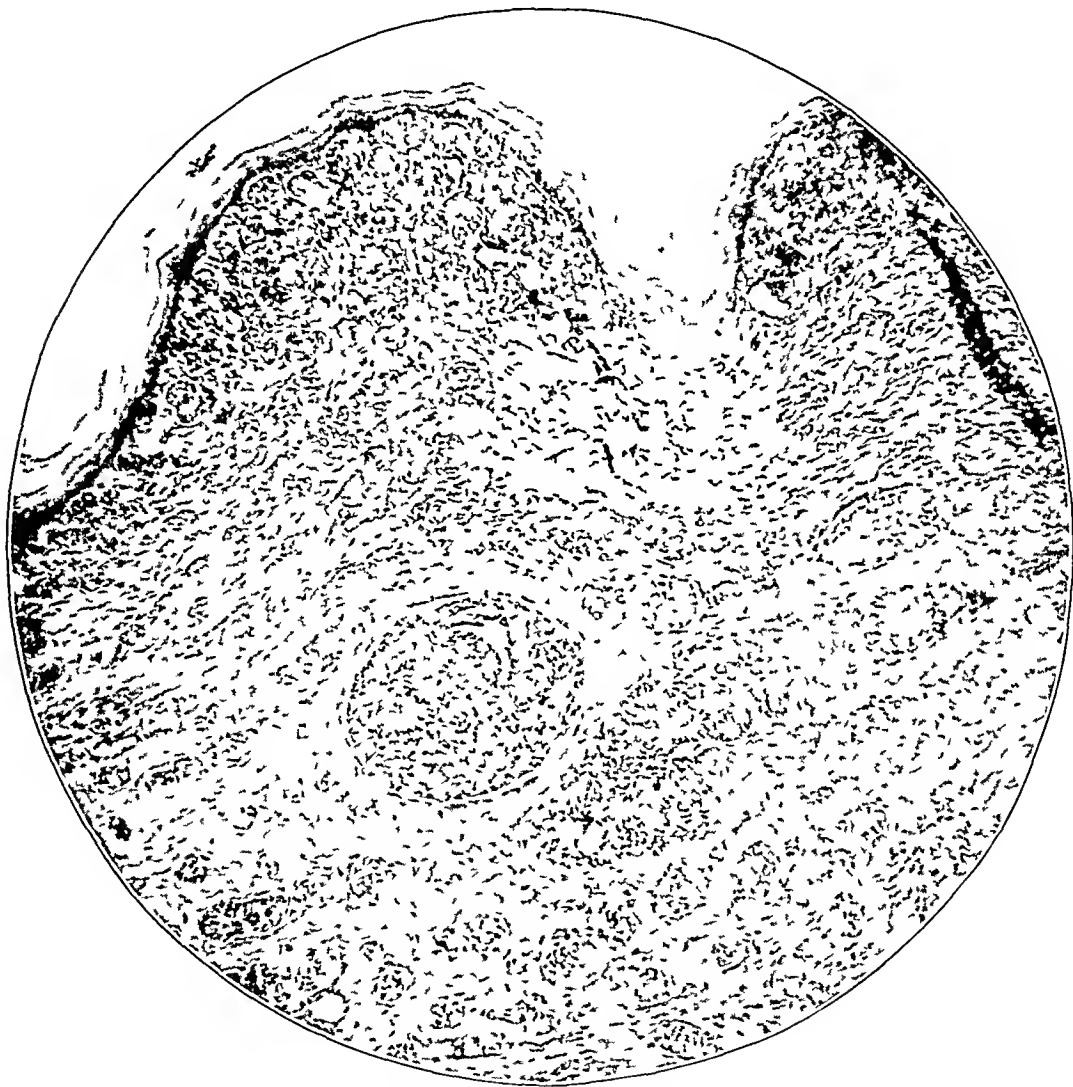


Fig 2—Section from the same comb as figure 1, but near to the tip of the posterior portion, proximal to a line demarcating gangrene. There is marked hyperemia throughout. The vessels are engorged, and the coats are stretched thin. The vessels contain old blood and degenerated blood pigment, evidence of the marked stasis noticed during life. The epithelial covering of the comb appears edematous. On higher magnification, the epidermal layer is slightly thickened. The marked interference with the circulation produced by the spasm of the artery (fig 1), and the marked dilatation and stasis shown in this picture, resulted in the dry gangrene about 3 mm distal to the place from which this section was obtained.

course this is also true of endemic ergotism. The frequent pathologic effects, such as trophic ulcers, edema, inflamed or indurated soft tissues, gangrene, atrophy, etc., are well understood, but there is no precise knowledge of the vascular and neural changes that precede these effects.

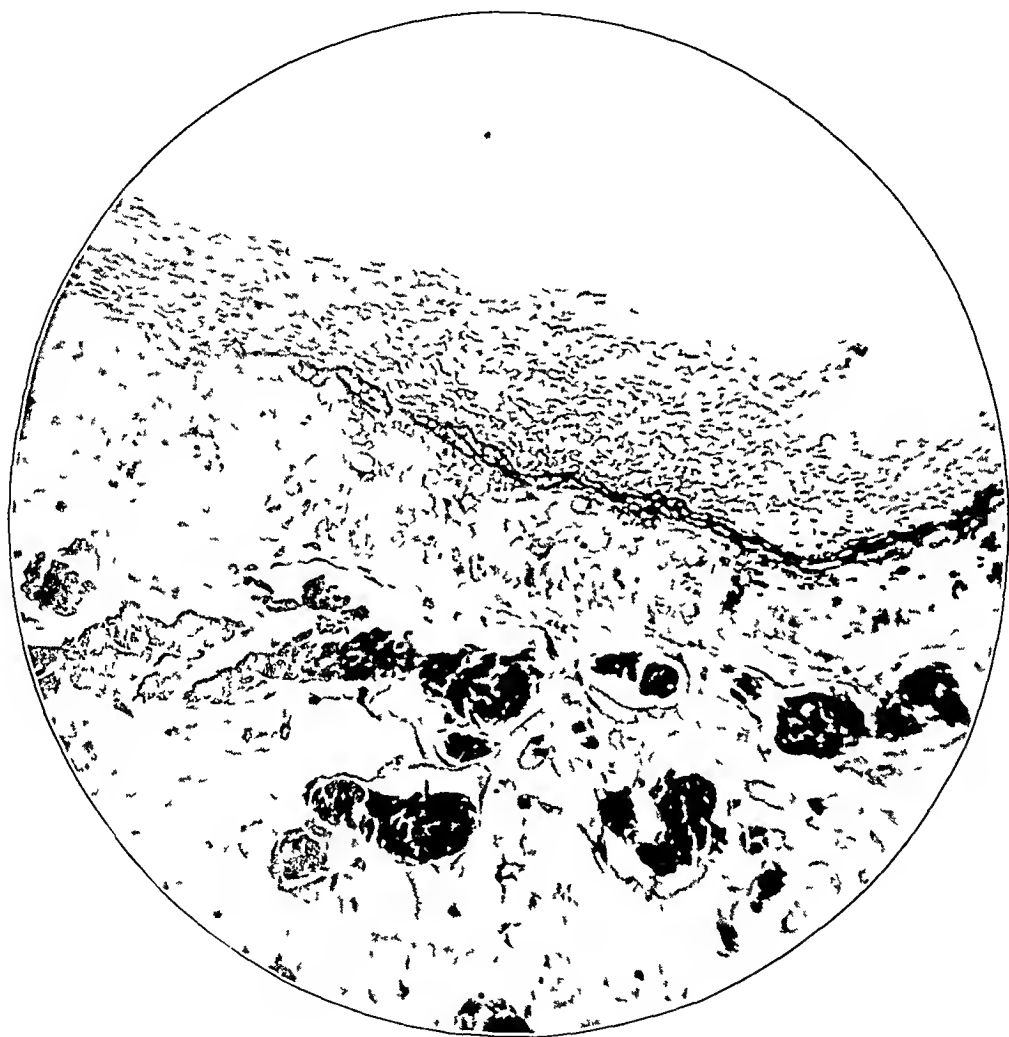


Fig 3—Chronic ergotism (about seven months). The section was taken from the middle of the posterior part of the cock's comb. Chronic edema, which is very evident in the dermis, is noted throughout the section. The thickened epidermis appears loosely attached. During life, this desquamated grayish scales. There were small capillary hemorrhages over the entire comb and a few ulcerations at its base. Some of the arteries appeared contracted and showed some intimal thickening. Absolute occlusion was not noticed in the vessels. The trophic changes were most probably due to the vascular dystonia. During life, the comb appeared pale at the base, slightly reddish in the middle and purplish at the tips, suggesting angiospasm at the base with dilatation and stasis at the periphery. The hard edema, scaling and vasomotor symptoms suggested the skin and subcutaneous changes described in cases of scleroderma and dermatomyositis.

Buerger,¹³ who made an extensive study of this subject, particularly of thrombo-angutis obliterans, expressed the belief that only the latter condition of this group is to be associated with any organic obliteration of the lumina of the vessel, the pathologic effects in the others arise

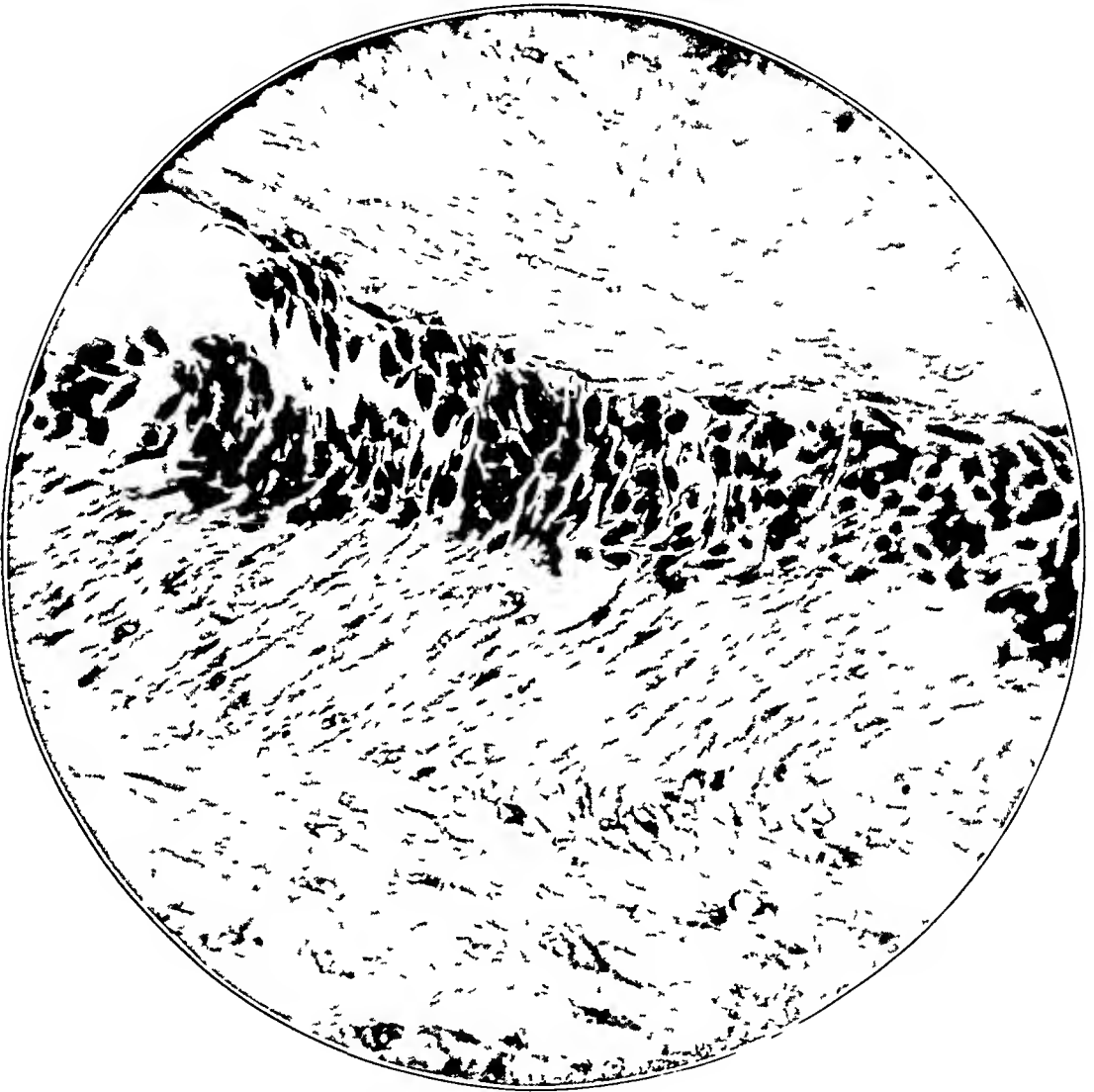


Fig 4—Chronic ergotism (about one year) The section was taken from the middle of the posterior portion of the cock's comb showing early hyperplasia of the intimal cells. Note the tendency of the cells to grow with their long axes radial, as in early thrombo-angutis obliterans. The oval cells in the lumen are erythrocytes, which are nucleated in birds.

only as a result of vasomotor and neurotrophic disturbances. Although there are many who concur in this opinion, there are others who attach considerable importance to endarteritic changes, particularly in some of the smaller arteries of the extremities in Raynaud's disease and erythromelalgia. Of course, in the absence of complete organic occlusion

¹³ Buerger, Leo. *The Circulatory Disturbances of the Extremities*, Philadelphia, W. B. Saunders Company, 1924, p. 376.

in these vessels, one must agree that additional factors are necessary to interfere with the circulation and produce trophic ulcers, chronic edema, gangrene, etc. The combination of arterial spasm and dilatation of the capillaries and venules results in a stasis, which could produce such pathologic lesions in the peripheral tissues, as I suggested. The organic changes in the vessels mentioned in the exhaustive studies of Isaac¹⁴ and those of Cassirer and Hirschfelder¹⁵ in patients with



Fig 5 — Chronic ergotism, simulating thrombo-angitis. This section was obtained about 2 mm proximal to the one shown in figure 4. This vessel shows the later stages of thrombo-angitis in which organization has occurred both in the intimal tissue and in an attached thrombus. The organization and fusion of both tissues makes it extremely difficult to differentiate them as separate entities.

14 Isaac, Georges Pierre. Contribution à l'étude de la pathogenie du syndrome de Raynaud (de l'importance des lésions artérielles), Thesis, Paris, L. Arnette, 1926, p. 88.

15 Cassirer, Richard D., and Hirschfelder, Robert. Vaso-motorisch-trophische Erkrankungen, Spezielle Pathologie und Therapie inneren Krankheiten, Berlin, Kraus & Brugsch, 1924, vol. 10, part 3, p. 579.

Raynaud's disease indicated that this disease is not merely a vasomotor condition. The same may be said of erythromelalgia in which endarterial and even thrombotic changes were found by Shaw¹⁶ and others. Benoist,¹⁷ backed by his experience and an extensive bibliography expressed the opinion that organic changes are found in the vessels as well as degenerative changes in the cord. Although the organic changes in these two conditions do not usually compare with those of thrombo-

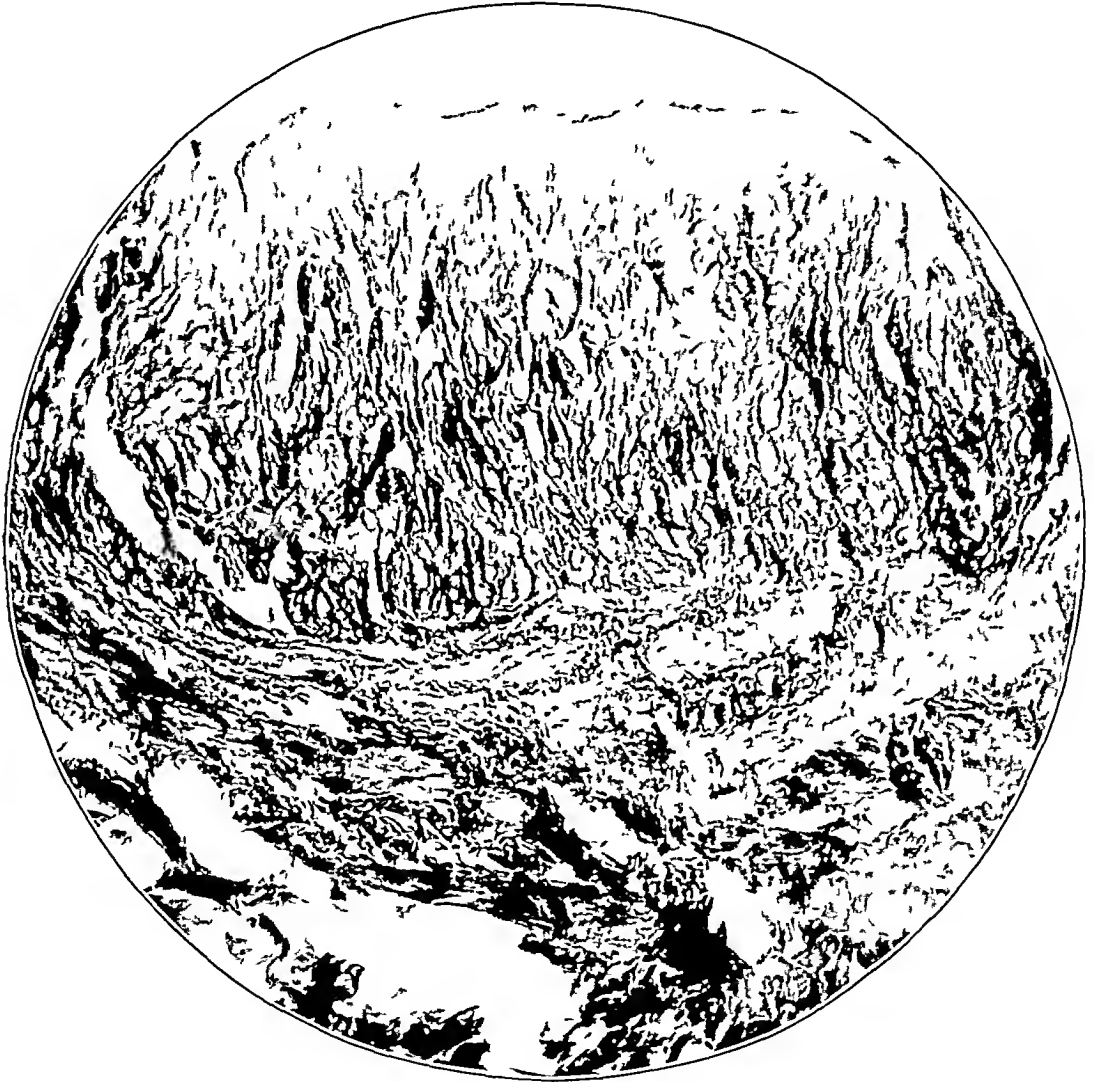


Fig 6—Section of a vein from a case of thrombo-angitis obliterans. Note the arrangement of the intimal cells with their long axes radial. This is an early stage in this process, although organization has already begun.

angitis obliterans, nevertheless they all may have a common causal relationship.

16 Shaw, H. Batty. The Morbid Anatomy of Erythromelalgia Based Upon the Examination of the Amputated Extremities of Three Cases, *Brit M J* **1** 662, 1903.

17 Benoist, Emmanuel. Étude sur l'erythromelalgie, Thesis, Paris, J. Rousset, 1911, pp 169-173.

The pathologic changes in ergotism are frequently mentioned, but usually without definite description. In spite of the many epidemics, knowledge on this subject is meager. Ergotism may be distributed to any peripheral portion of the body. Gangrene has been mentioned to have occurred in every part of the extremities and trunk, the viscera

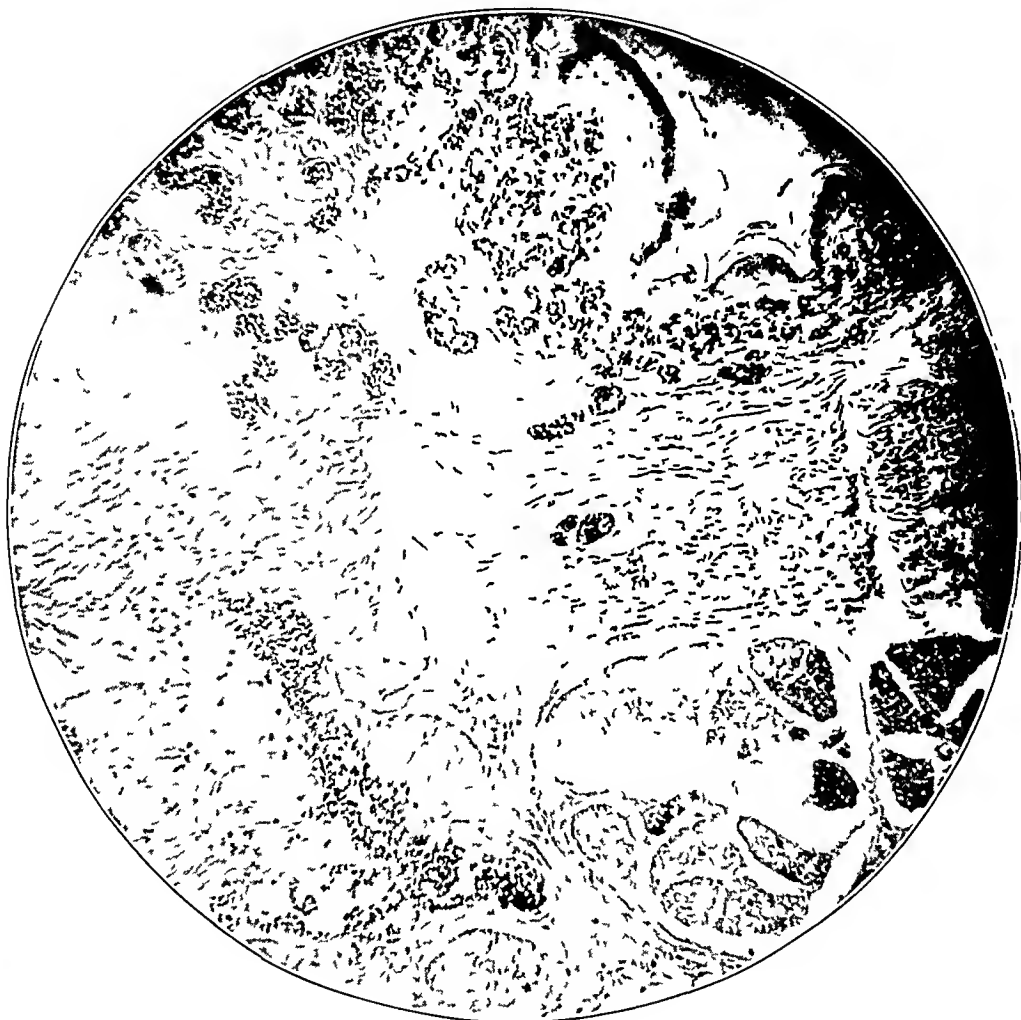


Fig 7—Acute ergotism. The section was taken through the skin, subcutaneous tissue and muscles of the rump of a rooster. Note the marked engorgement, particularly in the dermis. This condition appeared during life as a purpuric eruption. The marked stasis with deficient oxygenation probably accounted for this appearance. Other vessels are seen engorged in the subcutaneous tissues, some of which extend into the muscle fascicles. Many of these muscle fibers appear vacuolized in the transverse section.

and tips of the nose and ears. The report of an epidemic of acute convulsant ergotism at Viatka in 1889, written by Vinogradoff,¹⁸ who

¹⁸ Vinogradoff, N. F. Pathologic Anatomy of Ergotism, St. Petersburg, Vrach, 1895, pp. 585, 622 and 647.

found various types of vascular lesions in the viscera, contains perhaps the best description of these lesions. Nearly all of the large vessels contained thrombi, some of which were red, while others were composed principally of fibrin. In some of the smaller branches of the portal vein, organized thrombi were found. Some of the walls of



Fig 8—Acute ergotism in the same animal as in figure 7. The section was taken from the pectoral muscle, showing marked degeneration in the muscle fibers. Some fibers that appear least affected have lost the staining qualities of the normal, the striations not showing. There is marked engorgement in some of the vessels between the muscle fibers in other areas of this section. The skin that covered this area also had the purpuric appearance, as described in figure 7. Both of these lesions suggest an acute form of the more chronic disease, dermatomyositis.

the vessels were thickened with their lumina narrowed to such an extent as not to permit more than two or three erythrocytes to pass. Marked proliferation of the intima was observed in some of the vessels, while others showed fibrosis or hyaline degeneration.

In my experimental work, I was able to produce both acute and chronic eigotism in fowls. In the acute form, the arteries (fig 1) near the base of the comb were found contracted, and the media were swollen and hyaloid as though in a state of degeneration. On the other hand, the capillaries (fig 2) were markedly dilated, and contained stagnant

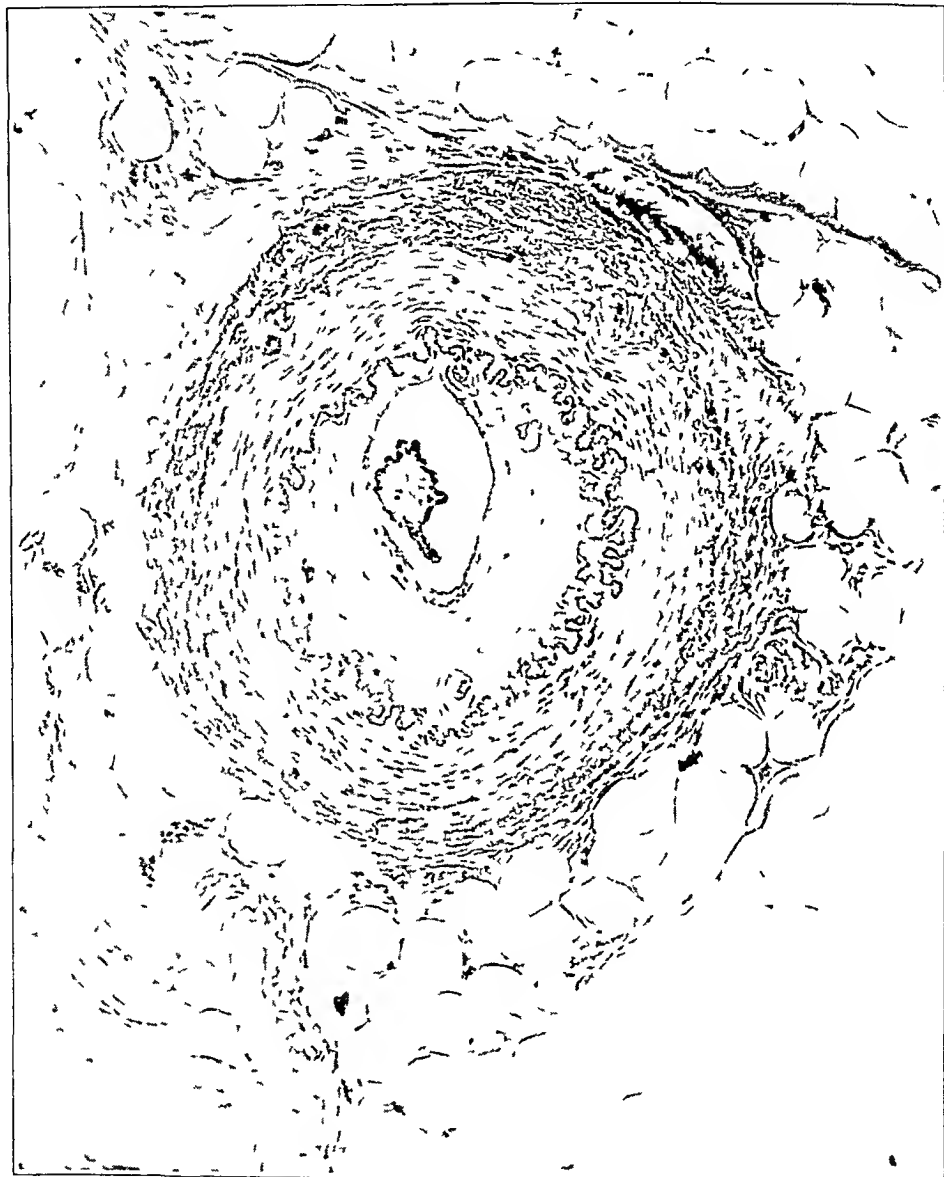


Fig 9—Photomicrograph of an artery from the finger in a case of Raynaud's disease reported by Cunningham (New York State J Med **26** 973, 1926). The artery shows a marked proliferation of the intima, which has become organized and contains newly formed vessels, as in thrombo-angitis. There was no evidence of actual obliteration of its lumen. One must interpret the gangrene that resulted as not being due to the organic changes in the vessels as much as to the vascular dystonia.

blood This stagnation was probably the cause of the gangrene at the posterior tip of the comb Evidence of stasis was also found in the skin and muscles of the pectoral and gluteal regions (fig 7) The capillaries in both the skin and muscles are markedly dilated, the latter showing evidence of degenerative changes

In a more chronic case, of about seven months' duration, in which many of the vessels of the comb showed endarterial hyperplasia, the comb was swollen to about double its natural width and manifested vasomotor and trophic conditions such as pallor, rubor, cyanosis (at the tips), ulcerations, fine capillary hemorrhages and desquamation of the epidermis (fig 3) In a rooster on which autopsy was performed a year after the initial feeding with ergot, many of the vessels of the comb (fig 4) showed endarterial hyperplasia with the intimal cells tending to grow with their long axes radial, as in thrombo-angitis obliterans, described by Mahorner¹⁹ Many vessels showed organization of the thickened intimal process, one artery (fig 5) showed an organized thrombus fused to the organized intimal process as in a later stage of thrombo-angitis obliterans

As no thrombus completely obliterated the lumina in the vessels of either the acute or the chronic ergotized animals, one must conclude that in these cases the destructive processes were due to the dystonic vascular conditions, that is, there was spasm in the arteries with dilatation and stasis in their terminal capillaries I suggested that, by its interference with the nourishment of the tissues, this condition is capable of behaving as an obliterating thrombus in an artery

That ergot is capable of producing such effects is not strange when one realizes that it contains such substances as tyramine, which causes marked arterial constriction, and ergotoxine, ergotamine and histamine, which cause marked capillary dilatation

One hesitates to attempt the unification of these vascular and trophic disturbances that have been so carefully classified as separate entities Classification dependent on symptomatic and even pathologic differences, however, should not interfere with a unification dependent on a common cause A difference in the lesions might depend on a difference in the ergot toxin and the idiosyncrasy of the host Such marked differences in pathology, clinical manifestations and distribution is possible in many diseases Such marked differences as between miliary tuberculosis and lupus vulgaris in tuberculosis make one realize the possibility that in ergotism there might be such dissimilar conditions as thrombo-angitis obliterans and scleroderma

19 Mahorner, H R Thrombo-Angitis Obliterans, in Brown and Allen, Mayo Clinic Monograph, Philadelphia, W B Saunders Company, 1928, p 54

Although occluding thrombi have not been obtained in our animals, one must remember that in human beings such thrombi have been described as occurring in ergotism, even in an organized state. Such observations, as well as the earlier vascular changes and the vasomotor and trophic conditions that have been demonstrated, might fit some cases of thrombo-angitis obliterans, Raynaud's disease or erythromelalgia. It may be that on closer scrutiny scleroderma, sclerodactylia, dermatomyositis, acro-asphyxia, etc., will show organic vascular changes.

The microscopic illustrations have been described with a view of showing the possible relationship between ergotism and the vasomotor and trophic diseases under consideration. It is hoped that they will help to clarify some of the important questions in this article.

CONCLUSIONS

1 Some etiologic factors, symptoms, physical signs and pathologic manifestations have been discussed about a group of vasomotor and trophic disturbances which includes thrombo-angitis obliterans, Raynaud's disease, erythromelalgia, acrocyanosis, scleroderma, sclerodactylia, dermatomyositis, etc.

2 The relation of this vasomotor and trophic group of conditions to ergotism in human beings and that experimentally produced has been considered.

3 It has been shown that ergot infests our rye fields, occasionally in dangerous quantities.

4 In a study of thrombo-angitis, it has been shown that in patients having this disease, rye bread forms a large part of the diet. A more careful study, which will correlate the diet with these vasomotor and trophic diseases, is necessary.

5 In view of our knowledge of the effects of toxic ergot, it appears advisable to employ more stringent prophylactic measures, even before there is absolute proof of my suggestion that many cases of vasomotor and trophic diseases are due to the ingestion of ergot.

MULTIPLE PULMONARY ABSCESES SIMULATING TUBERCULOSIS

CAUSED BY THE FRIEDLANDER BACILLUS

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AND

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CHICAGO

Acute pulmonary infections caused by the Friedlander bacillus group have been known since 1882 and 1883, when Friedlander¹ described the micro-organism and attributed to it the cause of pneumonia. After several years of controversy by various investigators, Fraenkel² in 1886 described the pneumococcus as the cause of pneumonia and assigned the Friedlander bacillus to the rôle of a secondary invader. So convincing was Fraenkel's work that many physicians accepted it without qualification. However, soon afterwards, in 1886, Weichselbaum³ showed that the bacillus of Friedlander caused 55 per cent of the cases in a series of more than 100 patients. It was nearly ten years before valid confirmation of this work was produced by others, although many believed in it.

Some of the most acceptable reports were given by Étienne,⁴ 1895, Comba,⁵ 1896, Smith,⁶ 1897, Thiroloix,⁷ 1897, Howard,⁸ 1898, Beco,⁹ 1899, Moisejew,¹⁰ 1900, Brinckerhoff and Thompson,¹¹ 1901, Kokawa¹²

* Submitted for publication, Sept 8, 1930

* From the Research Laboratories of the Municipal Tuberculosis Sanitarium

1 Friedlander Virchows Arch f path Anat **87** 319, 1882, Fortschr d Med **1** 175, 1883

2 Fraenkel Ztschr f klin Med **2** 437, 1886

3 Weichselbaum Med Jahrb **1** 483, 1886

4 Étienne Arch de med exper et d'anat path **7** 124, 1895

5 Comba Jahresb u d Fortschr d path Microorg **12** 101, 1896

6 Smith J Boston Soc M Sc **2** 174, 1897-1898

7 Thiroloix Bull et mém Soc anat de Paris **11** 152, 1897

8 Howard Philadelphia M J **1** 336, 1898

9 Beco Rev de med **19** 461, 1899

10 Moisejew Bolnitschanja Gazetta Botkina **11** 889, 1900

11 Brinckerhoff and Thompson Rep Boston City Hosp **12** 149, 1901

12 Kokawa Deutsches Arch f klin Med **80** 39, 1904

1904, Stuhlein,¹³ 1904, Apelt,¹⁴ 1908, Brissaud,¹⁵ 1912, Gouget and Moreau,¹⁶ 1912, Mosny and Pruvost,¹⁷ 1913, Sisson and Thompson,¹⁸ 1915, and Zander,¹⁹ 1919

Although there were numerous reports up to 1915, Sisson and Thompson saw fit to include only thirty-three cases as completely studied and acceptable, to which group they added four. Since then a few complete studies have been made, which include a large series by Zander.

The bacteriologic observations have not been entirely constant. All observers have noted a gram-negative, round-ended, encapsulated bacillus growing with the production of a characteristic viscid diffuent growth. In carbohydrates of this organism the growth reactions resemble those of the colon-aerogenes group, but they vary from one to the other in the methyl red, Voges-Proskauer, lactose fermentations and milk coagulation reactions.

The clinical and pathologic aspects are most commonly those of an acute infection with the corresponding symptoms and observations. Most of the early reports dealt with such infections.

Apart from the acute infections, however, the micro-organisms have been isolated from conditions of the lungs of varying grades of chronicity, some extending over a period of months and years and simulating pulmonary tuberculosis or some other chronic disease of the lungs. Étienne included in his group one patient from Banti's and one from Galvagni's clinic, who lived for several weeks. Apelt¹⁴ reported two fatal cases with large cavities, one undergoing a rib resection without avail. Cohn²⁰ reported one pulmonary abscess, but he did not state the outcome.

None of the older reports, however, conveyed the idea of chronicity that actually exists. In 1926, Belk²¹ reported a series of eighteen cases, of which two and perhaps three were chronic abscesses of the lungs of long standing. In 1926, Westermarck²² was the first to call attention to the similarity of the condition to tuberculosis, as shown in

13 Stuhlein Zentralbl f Bakteriöl 36 493, 1904

14 Apelt München med Wchnschr 55 833, 1908

15 Brissaud Lyon med 80 205, 1912

16 Gouget and Moreau Bull et mem Soc med d hôp de Paris 34 296, 1912

17 Mosny and Pruvost Bull et mem Soc med d hôp de Paris 35 395, 1913

18 Sisson and Thompson Am J M Sc 150 713, 1915

19 Zander, A Deutsche med Wchnschr 45 1180, 1919

20 Cohn Deutsche med Wchnschr 19 804, 1893

21 Belk, W P J Infect Dis 38 115, 1926

22 Westermarck, N Acta radiol 7 626, 1926

a case in which the patient lived for six months. The pathology and bacteriology were reported by Berglund²³. In 1927, Brulé and his colleagues²⁴ reported one case of nine years' duration in which the disease fluctuated between a chronic condition of the lungs and periods of quiescence. In 1929, Collins and Kornblum²⁵ reported three chronic infections of the lungs by the Friedlander bacillus with recovery, all of which resembled tuberculosis. To this brief list of seven or eight cases we wish to add another.

The patient lived for twenty-eight months after infection, and presented the observations of chronic pulmonary abscesses simulating tuberculosis.

REPORT OF CASE

History—W. K., aged 45, born in Poland, entered the sanitarium on Jan. 4, 1929. He had attended school for four years, had worked on a farm and had come to the United States at the age of 25. Since that time he had worked for a steel company. He smoked and drank with moderation. Except for slight colds and an operation for inguinal hernia, the past history was irrelevant. The present complaint dated from Sept. 28, 1927, when he "caught cold," following which he began to cough and to have a fever. There was a moderate expectoration that was sometimes blood-streaked, and the patient had lost 7 pounds (3.2 Kg.) in weight. His appetite was good, he slept and felt well, in spite of a rather severe productive cough.

Examination—General inspection revealed a moderately thin man with a pinkish-white skin that differed from the usual pale yellowish complexion of the tuberculous patient.

The chest presented the principal positive observations. It was fairly symmetrical with a slight lag on the left, the expansion was poor, tactile fremitus was increased bilaterally, more posteriorly, and there was dullness in the upper lobe of the right lung. The breath sounds were diminished over the upper right and were slightly increased over the left. There were a few persistent râles in the upper lobe of the right lung. The diagnosis was "pulmonary tuberculosis, moderately advanced B."

There was a very small amount of sputum at this time, and the patient gained 5 pounds (2.3 Kg.) after admission.

The roentgen examination reported by Dr. Carroll E. Cook on Jan. 15, 1929, was as follows. The apexes of the lungs lighted up poorly, the left better than the right. The costophrenic angles were clear. The cardiac shadow was within normal limits as to size, shape and position. At the hilus on the right, and extending upward and outward, there were mottled areas of increased density with definite evidence of several cavities, typical of active, far advanced, pulmonary tuberculosis (fig. 1).

On three subsequent examinations the picture was essentially the same, with more extensive involvement and cavity formation each time (fig. 2).

²³ Berglund. *Acta radiol.* 7:626, 1926.

²⁴ Brulé, M., Huguenin, R., and Gilbert-Dreyfus. *Bull. et mem. Soc. méd. d. hôp. de Paris* 51:1370, 1927.

²⁵ Collins, L. H., and Kornblum, K. Chronic Pulmonary Infection Due to the Friedlander Bacillus, *Arch. Int. Med.* 43:351 (March) 1929.



Fig 1—Roentgenogram of chest on admission, showing an involvement at the base of the right lung and cavities and infiltrations in the upper lobe of the right lung that are almost identical to a tuberculous process

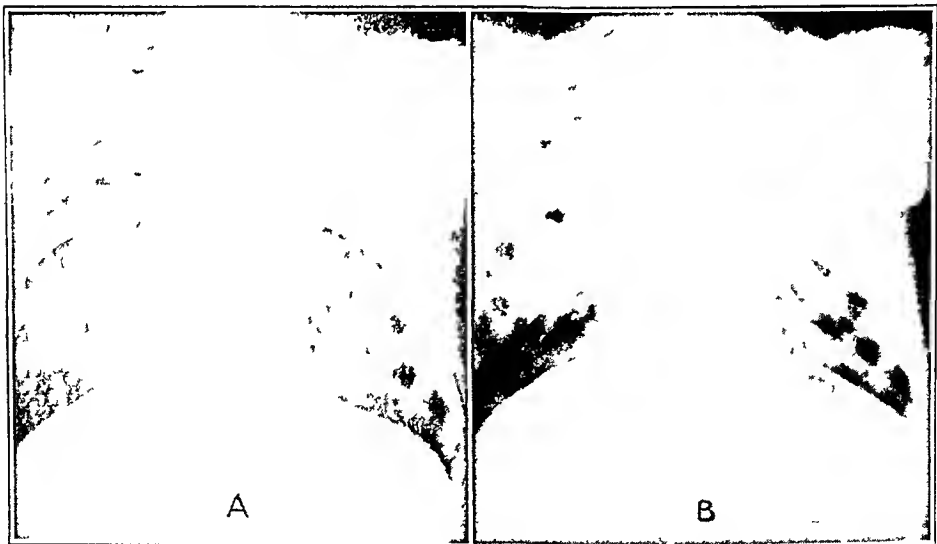


Fig 2—A, roentgenogram taken on Aug 5, 1929, eight months after admission, showing more extensive excavations on the right with large annular shadows with fluid levels and extension to the upper lobe of the left lung B, roentgenogram taken Dec 2, 1929, two months before death, showing a still further progress of the disease There is little to differentiate this from an advanced tuberculosis

Clinical Course—The patient improved until June, when he experienced a severe attack of coughing with pain in the chest, followed by profuse expectoration of a reddish-brown sputum containing peculiar brownish flakes. A persistent search for tubercle bacilli was negative. The odor was not offensive at this time. The cough was of a "brassy" type. Although following this attack there was evidence of extensive destruction of the lungs, the patient did not lose strength in proportion to the involvement, as occurs in tuberculosis. Even on the last day he was able to get up and brush his teeth. The physical signs also were not in proportion to the involvement shown by the roentgenogram. Toward the end the odor of the sputum became increasingly offensive. The temperature was very irregular, corresponding with what may have been septic exacerbations. Sometimes the pulse rate fell as the temperature rose, although not always.

The most important laboratory observations were the continued absence of tubercle bacilli in the sputum in six guinea-pigs, many cultures and more than eighty direct examinations, as well as the persistent finding of a heavy, mucoid, encapsulated bacillus that was tentatively considered a member of the *B mucosus-capsulatus* group. Urinalysis gave negative results, and the blood revealed only a moderate leukocytosis (13,000) with a mild anemia.

The patient died on Jan. 31, 1930, and a necropsy was performed within seven hours.

Necropsy Observations—The essential features observed were as follows. The body was that of a markedly emaciated white man, aged 46, 5 feet, 3 inches (160 cm) in height, weighing 105 pounds (47.6 Kg). Postmortem rigidity was present, and lividity was seen in the dependent portions. The pupils were equal and measured 5 mm.

The following observations were made on the thoracic cavity and lungs. The pleural cavities were completely obliterated by firm fibrous adhesions except at the bases. In the lower right side of the pleural cavity there was about 500 cc of a foul-smelling, greenish-yellow pus. The heart lay in the midline and was about the size of the patient's fist. The tracheobronchial lymph nodes were enlarged, and on cut section were grayish black, but showed no evidence of tuberculosis.

On section, the upper lobe of the right lung contained a large cavity toward the axillary angle, measuring 5 by 7 cm. The wall was grayish black and did not appear to possess the usual type of granulation tissue found in tuberculosis. The fibrous capsule over the apex was from 2 to 3 mm in thickness, and was perforated in a few places. Anteriorly this cavity communicated in a downward direction with a cavity on the anterior surface of the middle lobe. There was also a cavity in the lateral angle in the middle lobe, measuring 3 by 5 cm. There was a small early cavity in the inner border of the middle lobe that was in the process of formation, measuring 1.5 cm in diameter. In the lower lobe there were a few early cavities in the anterior portion with slight atelectasis toward the base, resulting from compression by fluid. There was an occasional infiltration of the secondary lobules ranging from small, early, grayish consolidations to larger areas of caseous bronchopneumonia with reddish central portions. Throughout the cut surface of both lungs there were numerous deposits of coal pigment measuring 3 mm in diameter and spaced about 7 mm apart.

The upper lobe of the left lung contained a large irregular cavity extending from the anterior through to the posterior aspect and measuring at different diameters from 8 to 10 cm across. It was partially filled with a grayish-pink, gelatinous pus. The lower lobe contained a few smaller cavities in the upper part, measuring from 1.5 to 2 cm toward the apex and decreasing in size toward

the middle of the lower lobe, where there were a few that measured from 7 to 10 mm. A few consolidations were present, as in the right lung. The base of the left lung was relatively normal (fig. 3).

The microscopic appearance of the lesions from the different parts of the lungs was as follows. An early lesion from the lower lobe of the right lung showed many alveoli filled with scattered fibrin shreds containing a few lymphocytes, monocytes, red cells and coagulated serum, undergoing varying stages of resolution with a superimposed necrosis. The fibrin was irregular in location. The centers of necrosis began at irregular intervals throughout the nodule and coalesced as the alveolar walls were broken down. The cellular content varied,

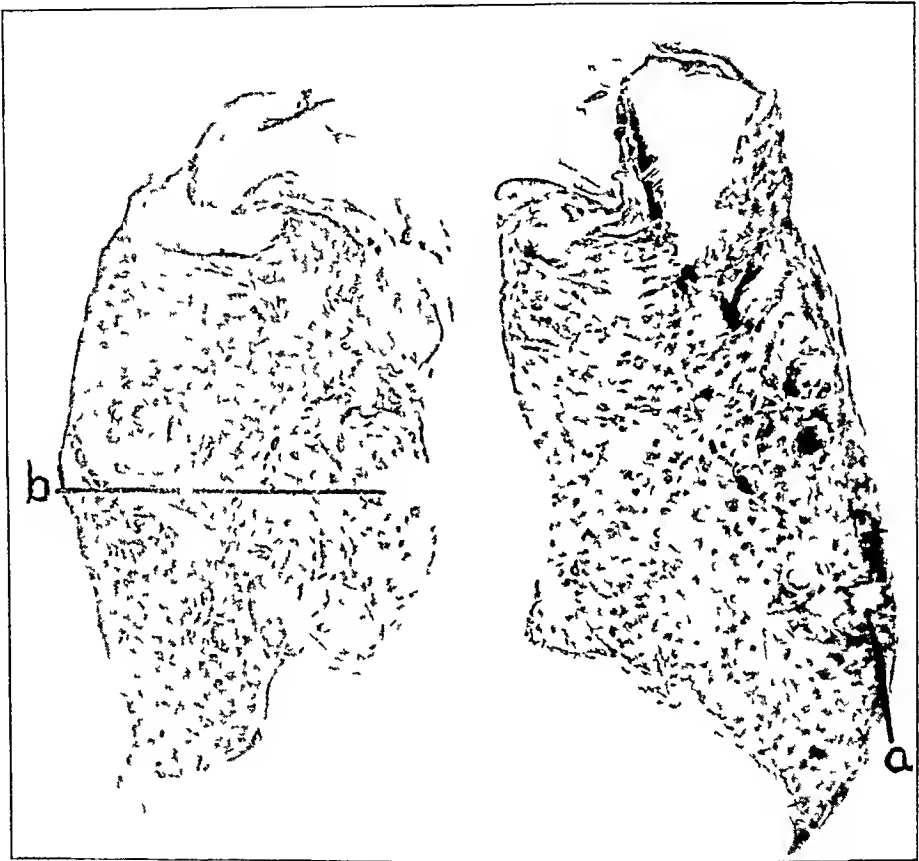


Fig. 3—Sagittal section of both lungs anterior to the bronchi, showing large cavities with partially epithelialized walls and smaller thin-walled cavities. The two small sections (a) and (b) have been removed from small foci of bronchopneumonia, which are represented in figures 4 and 5.

the majority of the nodules consisting of lymphocytes and plasma cells. Most of the blood cells in the alveoli were laked, and the vessels appeared engorged, bright red and homogeneous. In the older necrotic centers there were more polymorphonuclears, increasing in some parts to 75 or 80 per cent of the cellular content, and appearing like acute miliary abscesses superimposed on the more chronic lesions (figs. 4 and 5).

A moderately advanced lesion showed the walls of the alveoli broken through and most of them destroyed by necrosis, irregularly throughout the margin of the lesion there were layers of fibrin with only a few cells and laked red blood

cells packed within the remaining alveolar walls. Early ulceration was present in the interior. The border of the lesion was sharply demarcated from the surrounding lung tissue.

An advanced lesion showed the walls of the larger cavities in the upper part of the lower lobe composed of an irregular wall of granulation tissue, beneath which were burrowing miniature abscesses composed chiefly of leukocytes varying in the percentages of each variety in different locations. As a whole, the early formations were nearly all lymphocytes, but polymorphonuclears seemed to come later, and appeared to hasten the necrosis and ulceration.

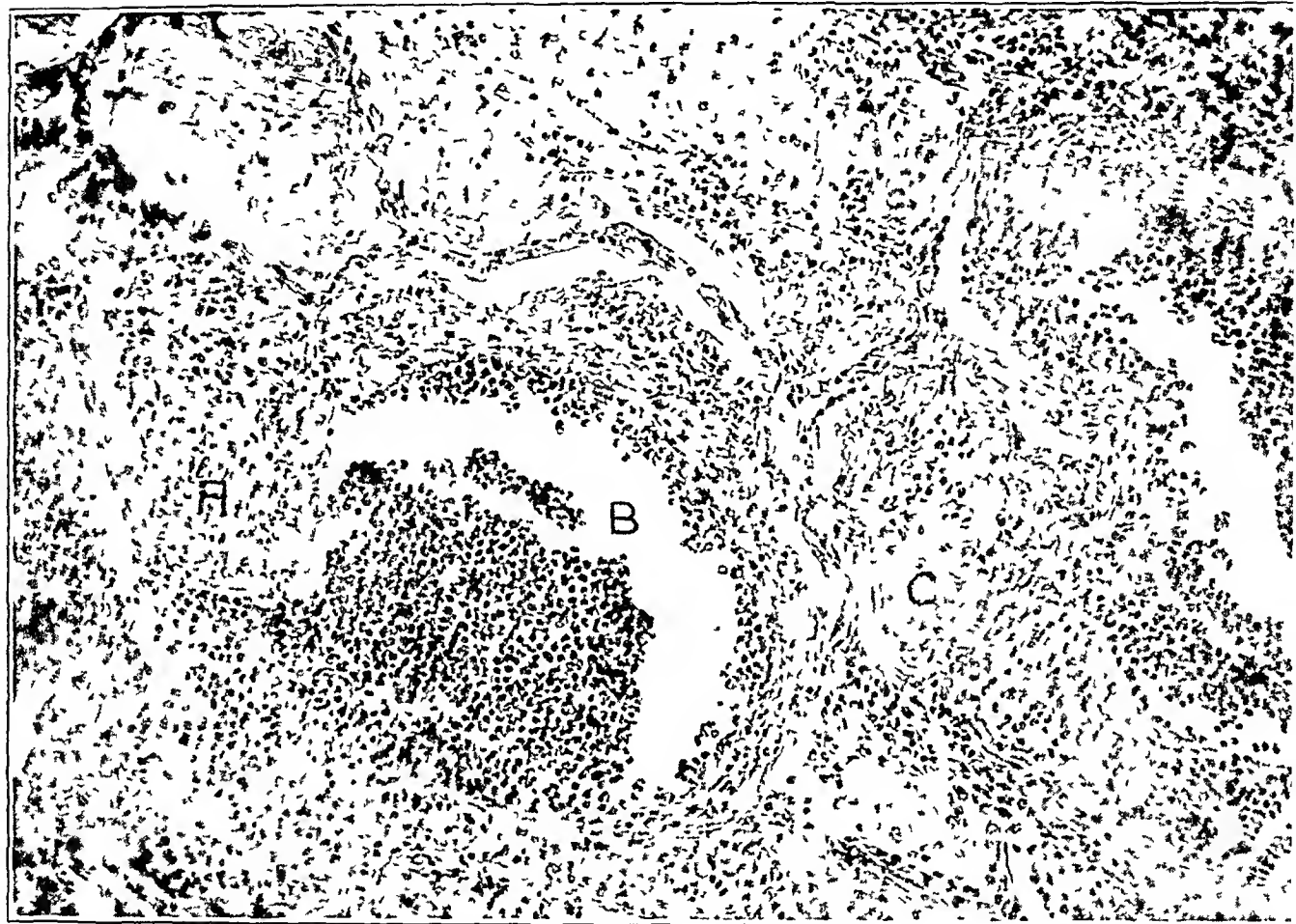


Fig 4—A high, dry, microscopic field of a bronchopneumonic focus, showing the beginning of the stage corresponding to gray hepatization. Some alveoli at *A* were filled with a thin material containing scattering monocytes and a few fibrin shreds. At *B* is an alveolus in which an infiltration of lymphocytes and polymorphonuclears has begun along the alveolar wall and has extended into the center of the mass. The alveolar wall shows a beginning disintegration at *C*. Hematoxylin and eosin stain, reduced from $\times 240$.

In a section of the wall from the inner to the outer border of the cavity there was a layer of loose debris composed of broken down cells of all types (polymorphonuclears, lymphocytes, monocytes, "foam cells," etc) and fibrin. Beneath this was a layer of granulation tissue about 0.5 mm thick, the inner border of which was necrotic and protruded in some places into polypoid projections which had layers of squamous epithelium over them in some places, and cuboidal or

columnar epithelium in others. In this layer were newly found blood vessels, some of which were engorged and apparently undergoing thrombosis. Many lymphocytes, a few polymorphonuclears, fibroblasts and more adult connective tissue were also present. Beneath this layer was a layer about 0.5 mm in thickness of compressed and extinct alveoli, with heavy strands of pinkish-stained connective tissue. In and beneath this layer were cells of all types: desquamated alveolar cells, "foam cells," phagocytes containing coal and iron pigment, with a blending into the abscesses described. Emphysematous blebs were occasionally present. The arterioles were undergoing endarteritis. On oil-immersion examination, many

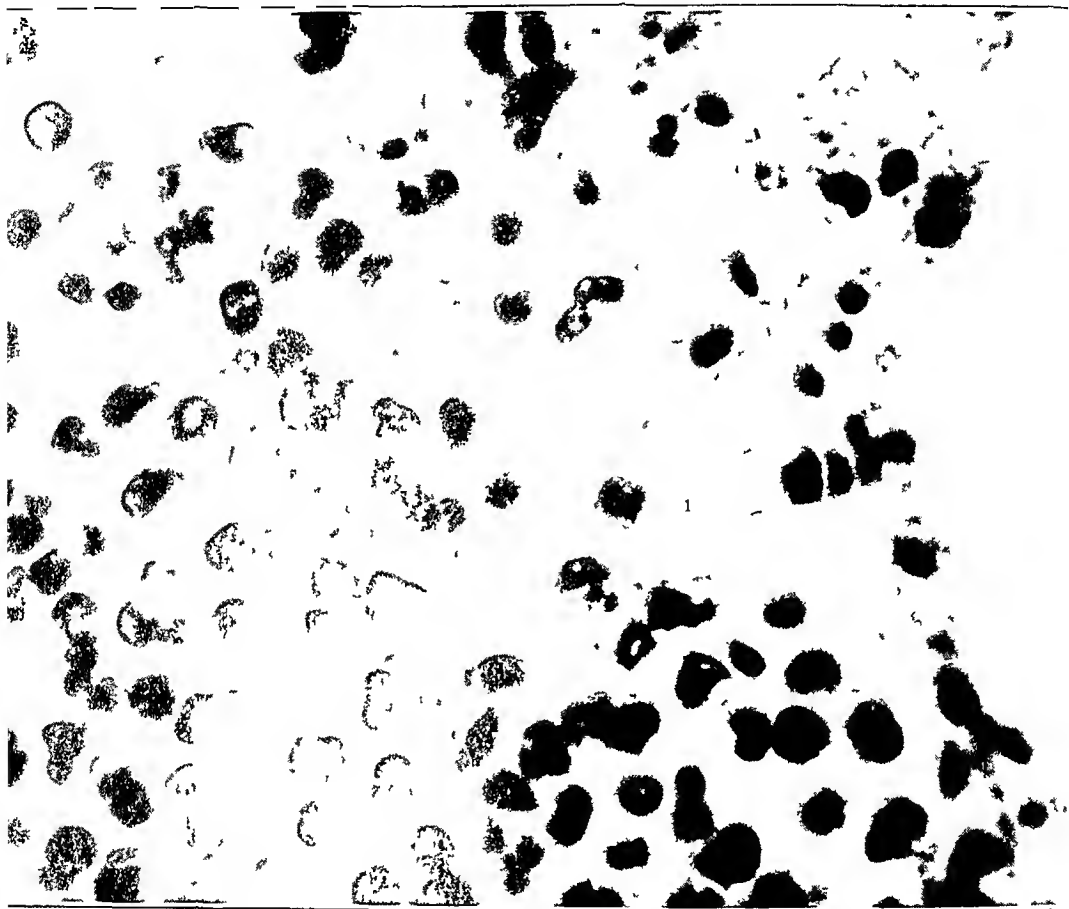


Fig 5—A high power view of the edge of a slough, showing polymorphonuclears and monocytes containing a few bacilli and numerous free bacilli. Gram stain, reduced from $\times 1,450$

round-ended bacilli could be seen, a few of which were observed within polymorphonuclears and monocytes. They had thick capsules when found within the monocytes and appeared like vacuoles containing bacteria (figs 6 and 7).

The bronchi draining the larger cavities and leading to the new foci had a mucosa that showed varying degrees of ulceration. In some places the mucosa was entirely denuded, with an infiltration of the submucosa with lymphocytes and only a few polymorphonuclears. A Gram stain of the section revealed numerous large gram-negative bacilli throughout the lesions. An acid-fast stain was negative for acid-fast bacilli.

The bacteriologic observations were of equal interest

While examining specimens of sputum, one could not help observing many heavily encapsulated bacilli with rounded ends. This micro-organism was present in the sputum in an almost pure culture, and there was no difficulty in isolating it. The same organism was isolated from the urine of the patient just a day before death, and once directly from the abscess of the lung at the postmortem examination.

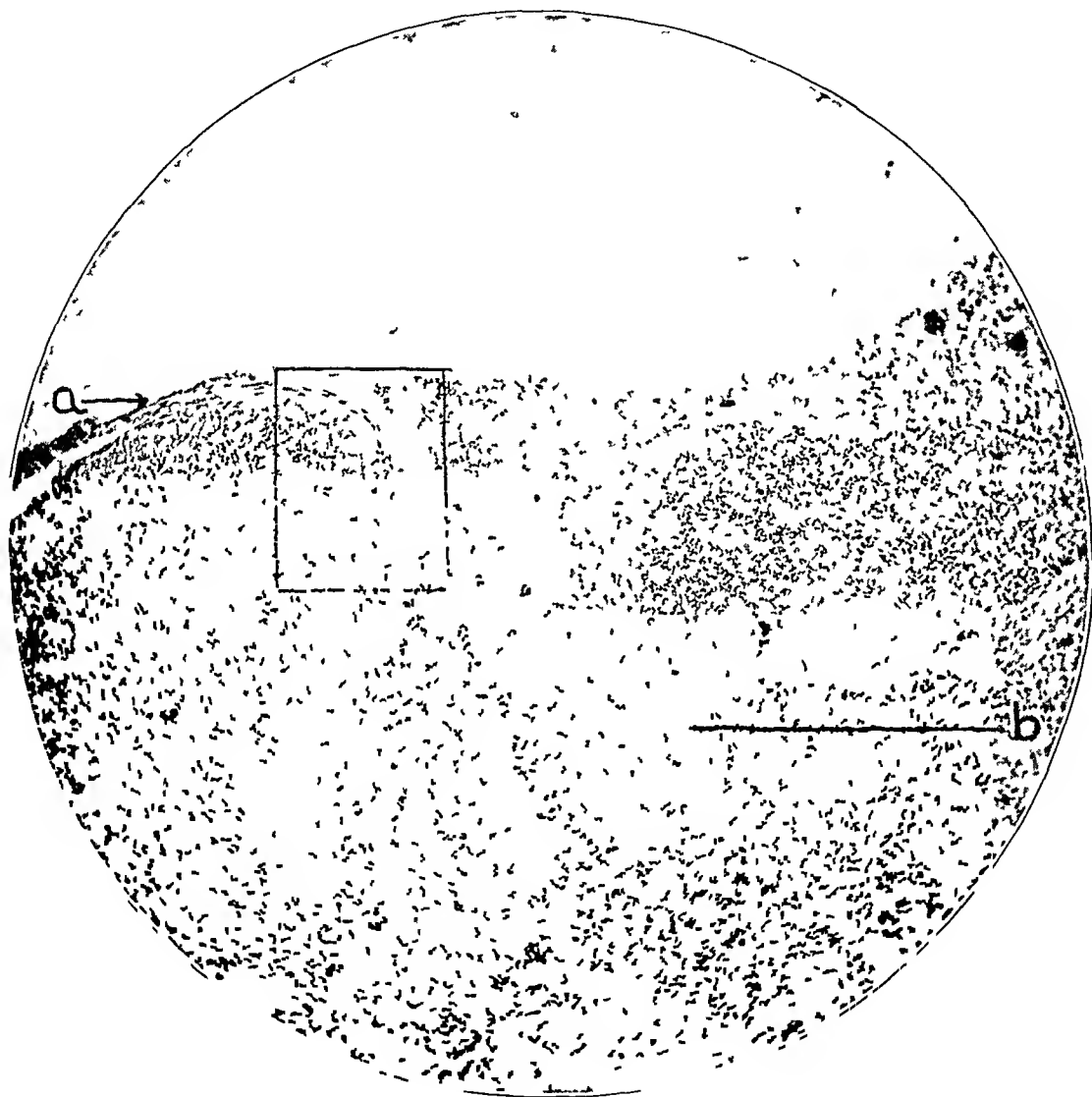


Fig 6—The wall of a large cavity, showing a simultaneous regeneration of epithelium by metaplasia at *a* and abscess formation at *b*. Hematoxylin and eosin stain, $\times 69$.

The micro-organisms isolated from the sputum, urine and abscesses of the lungs were identical in every respect. The cultural studies were made from a single colony fished from a twenty-four hour lactose plate.

The fermentation of carbohydrates was studied on agar slants containing 1 per cent of the carbohydrate and the double indicators—bromcresol purple and cresol red. It fermented arabinose, rhamnose, xylose, dextrose, galactose, levulose, lactose, maltose, sucrose, salicin, glycerin, mannitol, sorbitol and adonitol with

acid and gas, both aerobically and anaerobically. Raffinose and starch were fermented only in the butt aerobically, but throughout anaerobically. Dextin, inulin and dulcitol gave negative reactions.

It is interesting to note not only that the micro-organism grows as well anaerobically as aerobically, but that the reactions in carbohydrates were found to be more pronounced while the organism was growing in anaerobic conditions. This was especially noticeable in the beginning. Other details of the biology of this micro-organism were as follows. The Gram stain was negative. The growth on agar slants was very mucoid, stringy and almost diffuent. Litmus milk was acidified within from eighteen to twenty-four hours, and coagulation took place

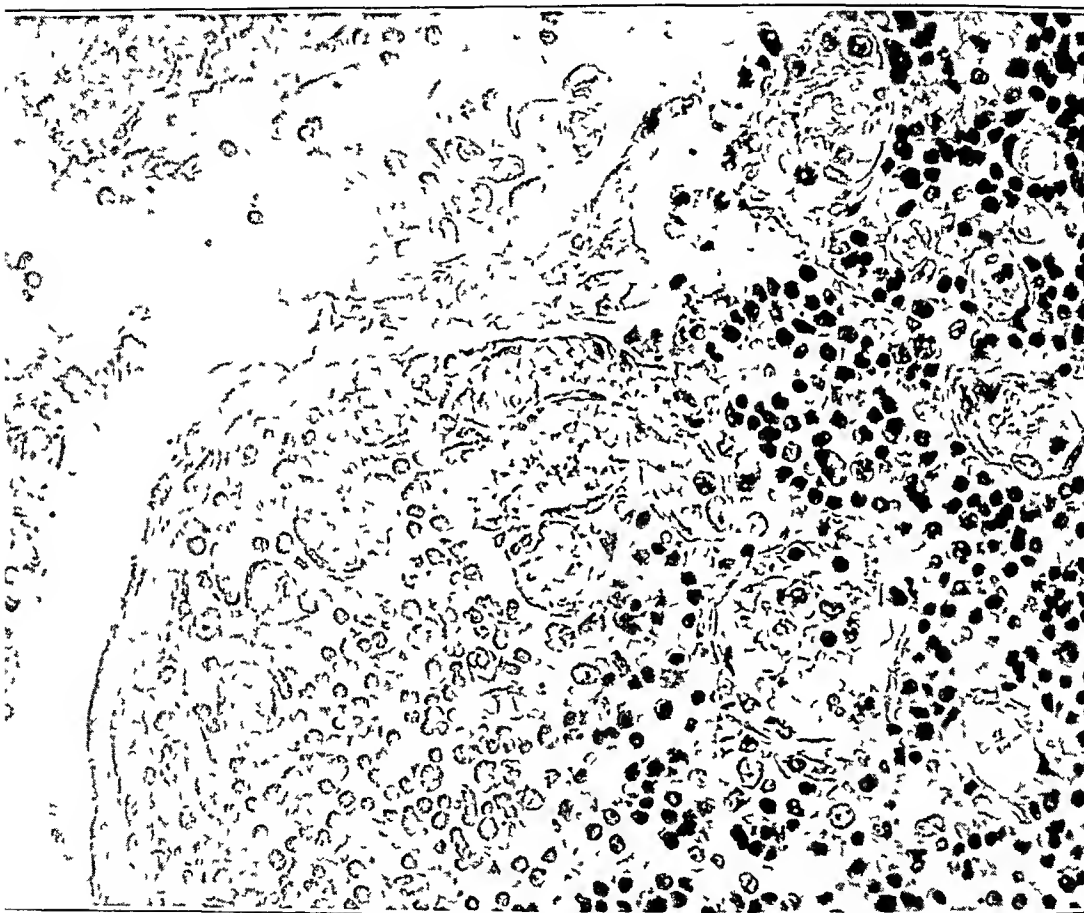


Fig 7—A higher magnification of the metaplasia of epithelium, showing the field outlined in the rectangle in figure 6. Hematoxylin and eosin stain, reduced from $\times 470$.

after forty-eight hours. Indol was not produced. Nitrates were reduced to nitrites. Urea was not decomposed. The methyl-red test gave positive results. The Voges-Proskauer test gave negative results. Citrate was utilized. These last three tests were repeated eight times, always with the same results. Gelatin was not liquefied. The growth had a typical "nailhead" appearance. Hydrogen sulphide was not produced.

The motility was studied with broth cultures. Examination of hanging drops was made after eight, twelve, fifteen and eighteen hours of incubation, and all of the tests gave negative results.

Capsules were easily seen in the specimens of sputum with the methylene blue (methylthionine chloride, USP) stain. However, while the properties of this organism were studied, it was grown on milk agar slant for eighteen hours, and was then examined for the formation of capsules by the india ink method. With this preparation wide capsules were observed. Hemolysis was not produced. Growth appeared within twenty-four hours on potato, but growth was poor on this medium. There was no formation of gas.

Pathogenesis—Mice, rats, guinea-pigs and rabbits were inoculated with broth culture. The mice died within from thirty-six to forty-eight hours after the subcutaneous injection of 0.1 cc. Subcutaneous injection of 0.5 cc killed rats within three days. An intraperitoneal injection of 1 cc killed guinea-pigs within thirty-six hours, while on subcutaneous injection only local abscesses developed, which ultimately healed. Intravenous injection, it seems, is only slightly pathogenic for rabbits.

Cultures from the heart's blood of mice, rats and guinea-pigs always yield a luxuriant growth of gram-negative bacillus, identical to the one that was inoculated.

Pathologic Observations—The pathologic condition in mice and rats was similar. There was an extensive edematous infiltration for 1 or 2 cm around the needle puncture. The peritoneal cavity contained a mucoid pus. There were miliary abscesses in the liver and kidneys, the spleen was slightly enlarged and dark red. The lungs were hemorrhagic, but not consolidated. There were cystitis and pyelitis.

From the various observations we were able to give an abbreviated anatomic diagnosis, as follows: chronic multiple pulmonary abscesses of both lungs with progress toward the base, presenting various stages of evolution from small foci of bronchopneumonia to large, thick-walled cavities, produced by encapsulated micro-organisms belonging to the Friedlander bacillus group, empyema of the right pleural cavity, with fibrinous pleuritis and atelectasis of the base of the lungs, obliterative pleuritis of the apexes of both lungs. Other incidental observations were hypertrophy and the deposit of coal pigment in the tracheobronchial lymph nodes, brown atrophy of the heart, slight fatty changes and marked passive congestion of the liver, spleen and kidneys, cloudy swelling of the liver and kidneys, acute splenic tumor, slight hyperplasia of the thyroid and atrophy of the prostate and right testis.

COMMENT

The feature of the case reported is that it represents a chronic type of infection with Friedlander's bacillus, which may be represented by a series of infections ranging from one day to many years. It seems logical, therefore, to follow the time-honored system of dividing the process into acute and chronic phases.

In order properly to understand the latter, it will be of advantage to detail the important observations in the former. The most complete work on the acute disease has been done by Moisejew, Kokawa, Stuhlern, Brissaud and his colleagues, Apelt, and Sisson and Thompson, among others, each group of which reported a series of cases. Some of their observations will be described, especially the pathologic ones.

In 1900, in reporting five cases, Moisejew¹⁰ compared this type of pneumonia to the three stages of croupous pneumonia, and showed striking and characteristic differences. This form begins without a true stage of red hepatization. Although a few fibrin plugs and red blood cells may be present, the cut surface is generally gray, semitransparent, nongranular and viscid from the beginning, owing to the masses of encapsulated bacilli and thick mucoid capsules. On fresh section there is a "burnt-meat" odor. Secondary foci of hepatization arise from the primary, and undergo the same stages of evolution, which have the following characteristics: the alveoli are dilated, with a granular edema containing scanty fibrin, scattering leukocytes and "alveolar cells" (monocytes) with many bacteria in their protoplasm. The blood vessels are engorged, especially on the periphery of the hepatization. Some alveoli contain blood. In the next stage, corresponding to the stage of gray hepatization of croupous pneumonia, the gray centers are due to the leukocytes invading the alveoli, usually along the walls, leaving the central mucoid mass. The blood vessels become constricted, and the alveolar walls become infiltrated with leukocytes. Necrosis finally develops, owing to this avascularity. In the red peripheral zone, the alveoli are of different sizes, and contain a recent cellular exudate, bacteria, mucoid masses and red blood cells. The alveolar walls are thinner and contain less leukocytes, but the capillaries are filled with blood that becomes coagulated and plugged with fibrin, and ultimately form solid thrombi that lead to necrosis, hemorrhage and abscess. This corresponds to the state of resolution of croupous pneumonia.

In 1904, Kokawa¹² reported work on fourteen cases, nine of which were complete. Although his observations differed from those of Moisejew in certain features, there was a common likeness. Kokawa stated that the cut surface is granular. As a general rule, there is less fibrin than in ordinary pneumonia, but there are still enough fibrin plugs to give a granular appearance in places, but not enough to give it the appearance of lobar pneumonia. He described the irregular position of the fibrin around the walls of the alveoli and through the "pores." He also emphasized the red coloration more and perhaps gave a more comprehensive idea of the condition, due, no doubt, to his greater amount of material.

In 1912, Brissaud and his colleagues¹⁵ reported nineteen cases and added little to what had been given before. They grouped the cases in three groups, namely those like true lobar pneumonia, those like confluent bronchopneumonia, and, the most common, those that are called pseudopneumonia, in which a large part or all of a lobe may be involved as one focus, but in which the borders are irregular and distinct from a lobar process. These authors expressed the belief that the observations are rather specific and characteristic.

In 1915, however, Sisson and Thompson,¹⁸ in reporting four cases said that they thought that no one feature may distinguish this form of pneumoma from the pneumococcus type, yet certain characteristics taken together will make the process easy to recognize. Their observations in general agree with the others mentioned.

From a clinical standpoint the disease is not so definite. Brissaud cited Letulle and Lumière, who divided it into two clinical groups: (1) atypical "pseudopneumonia," as previously described, and (2) like typical pneumonia, with recovery (Wiens, Schmidt), following surgical intervention and recovery (Lenhartz), or, more commonly, by death.

The physical findings reported are meager; Weill²⁶ and his co-workers reported the findings only of engorgement with absence of flatness, breath sounds and subcrepitant râles. These atypical observations are due no doubt to the mucoid material that obstructs the smaller air passages. The same author reported that the involvement shown by Roentgen shadows is not the triangles typical of pneumonia, but is more circumscribed.

The clinical course of the disease is often characteristic. There are usually a sudden onset and a rapid course (from two to five days), and usually there is no chill or herpes labialis. The temperature is usually irregular, there are a profound intoxication, cough, pain in the side and a pinkish-brown sputum containing encapsulated bacilli within and without the monocytes. Dyspnea is a constant, grave symptom. Death comes suddenly. The opinions of many physicians may be summarized in the words of Sisson and Thompson, who said that "General weakness, coma, signs of cardiac and respiratory failure all come suddenly and are outspoken. The frequency of the various lobes involved is of little importance. The outcome is nearly always fatal, death coming with little premonition."

Some authors, namely Netter, quoted by Étienne (twelve cases), Brissaud (nineteen cases) and many others, considered it always fatal. Lord²⁷ said that in no established case had the patient ever recovered. On the other hand, Zander¹¹ reported an epidemic in which only 35 per cent of the patients died. This report is striking in that the disease assumed epidemic proportions, and for that reason should be looked on in a different light than the sporadic unfavorable cases in which the mortality rate is very high. Therefore, it does not seem justifiable to consider every case of Friedlander's pneumoma as fatal because the early complete reports are on fatal cases. It is not consistent with

26 Weill. *Lyon med.* **122** 133, 1914.

27 Lord. *Diseases of Bronchi, Lungs and Pleura*. Philadelphia, Lea & Febiger, 1915, p. 234.

the epidemiology of the disease and besides many recoveries are not studied or even suspected. As we have mentioned, many cases become chronic, and in some the patients are reported to have recovered.

The chronic type of infection, the one about which we are most concerned in this report, is relatively less common. It is variable in its course. The clinical and pathologic manifestations vary from the acute form previously described to a chronic fibroid disease of years' duration. Many authors speak of a tendency toward the formation of abscesses, but references to such a symptom are not common in cases in which complete work has been performed. Only the relatively recent work is sufficiently complete to give a clear idea of the type of chronicity assumed by some of these infections.

In 1926, the cases of Belk²¹ were completely recorded, except that no protocols were given to show the type of micro-organisms present further than a "*Friedlander bacillus*." He mentioned one important characteristic that is omitted by most authors, namely, that the abscesses are not foul-smelling. This is true at the beginning. Moisejew and others mentioned an odor of burnt meat in the fresh specimen, but the chronic lesion seems to have little odor until late in the disease.

In the case of Westermarck, reported by Beiglund, there was a relatively complete bacteriologic and pathologic report. From this patient a micro-organism was isolated from a prostatic abscess. It produced an abundant, yellowish-gray, glassy growth on potato. The author did not mention the formation of gas. Dextrose bouillon is the only sugar mentioned, and that sugar produced acid and gas. There was a typical nailhead growth on gelatin. It was pathogenic to mice, rabbits and guinea-pigs intraperitoneally, but one rabbit survived subcutaneous injection. The dosage was not stated. Other culture reactions are characteristic or are not reported, which is true for the Voges-Proskauer and methyl-red reactions.

The gross pathologic changes were rather characteristic of a confluent bronchopneumonia with abscess formation. Microscopically, the alveoli contained an exudate consisting of polymorphonuclears, "alveolar epithelium" and a few lymphocytes. There was a thin network of fibrin, and in places there were many red blood corpuscles. Many alveoli contained masses of encapsulated bacteria. The alveolar walls were destroyed in places, and only leukocytes, bacteria and mucus were found. The walls of the cavity consisted of well differentiated bundles of collagen-bearing connective tissue. No remnants of bronchial walls could be found in the walls of the cavity. There was no evidence of tuberculosis. This report resembles ours, so far as the data given are concerned.

In 1927, Biule, Huguenin and Gilbert-Dreyfus²⁴ reported a case that began with a chill, pain in the side, dyspnea, elevation of temperature

cough and expectoration of a greenish sputum several times a day. The condition gradually became worse, the sputum became bloody, and the course extended over a period of nine years with numerous remissions. A rather characteristic Friedlander's bacillus was isolated, a vaccine from which seemed to help somewhat, but the improvement was not permanent. On physical examination during the patient's last illness, a normal percussion note was observed, the right side was painful on palpation and dry râles were noted on the left side opposite the vertebrae and at the base with a bronchial souffle at the apex. On the right there were rhonchi that changed to sonorous râles on subsequent examinations. Patches of fine râles were heard at certain places. Roentgen observation showed a uniform gray on the left, and a brushlike shadow at the base of the right lung, which suggested bronchial dilatation. The upper lobes were opaque, but not homogeneous, with a gray apex and a dark shadow beneath, which without careful roentgen observation would be considered an incisural lesion.

The gross pathologic observations revealed lesions of a chronic emphysema of the lungs with dilated bronchi and cavities blending into acute foci of bronchopneumonia. Microscopic lesions were characterized by peribronchial fibrosis with numerous lymphocytes and plasma cells. The epithelium was normal, flat or in layers showing true metaplasia. In the fibrotic apex of the right lung there was marked vascular and parenchymal sclerosis with lymphocytes, plasma cells and miliary foci of polymorphonuclears. The lesions appeared in crops or "échelons."

Collins and Kornblum²⁵ discussed the acute type in which death intervenes within from twenty-four to forty-eight hours, and reported three cases of the chronic type. The roentgen observations showed lesions of bronchopneumonia that were gradually coalescing to form pseudolobar pneumonia. It differed from the lobar form in not being so dense, it was not limited to one lobe, and was more intense at the periphery. The cavities were thin-walled and differed from those seen in any other condition except perhaps in chronic influenza. In the healed cases there was marked fibrosis. The authors divided the process into four stages: bronchopneumonia, pseudolobar pneumonia, abscess formation and fibrosis. They believed that the chronic process should be considered a disease entity.

Bacteriologically, the micro-organism that we isolated did not correspond in every way to the usual type of Friedlander's bacillus. The typical mucoid growth on agar, the presence of large capsules, the inability of the organism to liquefy gelatin or to produce indol and the source from which this organism was isolated suggested that it is closely related to *B. pneumoniae* of Friedlander. There is however, considerable controversy as to what should be considered a typical strain

of Friedlander's bacillus. Many authors (Strong²⁸ in 1899, Perkins²⁹ in 1904, Howard⁸ in 1898, Wilde,³⁰ and Coulter³¹ in 1917) described the typical strain as lactose-negative, while others (Grimbert³² in 1896, Nicolle and Hebert³³ in 1897, and Topley and Wilson³⁴ in 1929) considered it capable of fermenting lactose with acid and gas, and there are still others (MacConkey³⁵ in 1905, and Castellani and Chalmers³⁶ in 1919) who reported acid but no gas in lactose. Authors who considered the typical strain of *B. pneumoniae* of Friedlander to be lactose negative reported it also as not capable of producing coagulation in milk. Our strain constantly produced acid and gas in lactose, and coagulated milk within forty-eight hours.

Then it is not clear whether a typical strain should be methyl-red negative and Voges-Proskauer positive, or vice versa. There are disagreements on this point among certain authors. Our strain gave a positive reaction to the former and a negative one to the latter. It also utilized citrate, which is unusual for a strain that does not give a positive reaction to the Voges-Proskauer test. However, the last observation is in accord with the observation of Edwards,³⁷ who stated that the relation of the methyl-red and the Voges-Proskauer tests to citrate, which usually exists in the *B. coli-aerogenes* group, has not been demonstrated with strains of encapsulated bacilli from human sources.

In conclusion, infections by the Friedlander bacillus should be considered chiefly from the standpoint of a rather extraordinary parasite. The most important factors seem to be (1) the large number of bacilli with their heavy mucoid capsules that act as a foreign body and are difficult to cope with and (2) what appears to be a toxin of variable but undoubted potency. As a result, the different strains possess different degrees of virulence for each host, and, owing to this difference no doubt, the disease runs a fulminating, a subacute or a chronic course.

All of the various types of the disease (lobar, confluent lobular, lobular or "pseudo" pneumonia) present the same general observations with

28 Strong. Centralbl f Bakteriöl 25 49, 1899

29 Perkins. J Infect Dis 1 241, 1904

30 Wilde. Centralbl f Bakteriöl (pt 1) 20 681, 1896

31 Coulter, C. B. J Exper Med 26 763, 1917

32 Grimbert. Ann de l'Inst Pasteur 9 840, 1895, 10 708, 1896

33 Nicolle and Hebert. Ann de l'Inst Pasteur 9 67, 1897

34 Topley, W. W. C., and Wilson, G. S. The Principles of Bacteriology and Immunity, New York, William Wood & Company, 1929, vol 1, p 461

35 MacConkey. J Hyg 5 333, 1905

36 Castellani, N., and Chalmers, J. E. Manual of Tropical Medicine, London, Ballière, Tindall & Cox, 1919, p 934

37 Edwards, P. R. J Bact 15 245, 1928

only two variable factors, namely, the extent and the age of the lesions. The typical course of the lesion, whether it is a small lobule or a whole or a part of a lobe, is an invasion of the mucoid bacilli into the bronchioles and alveoli, with the prompt exudation of a thin fluid containing scanty fibrin and a moderate number of monocytes that promptly begin to engulf the bacilli. These phagocytes appear stuffed with the vacuoles of mucus that coalesce as the bacilli are destroyed. The alveolar blood vessels then become engorged with red blood cells, and some of them rupture in places, leaving scattering red corpuscles. This corresponds to the red stage of hepatization in pneumococcus pneumonia. It rarely has an appearance of a true red hepatization, but is a more smooth, slimy, yellowish gray, with a dark red zone where the blood vessels are engorged and ruptured. The red color is due to the engorged blood vessels, the true hemorrhage and the scattering fibrin, and not to the extensive fibrin and extruded red blood cells as in pneumococcus pneumonia. Following this "red" stage is what corresponds to the gray stage in which polymorphonuclears infiltrate along the alveolar walls and penetrate the alveolar plugs as well as the alveolar walls, where a tremendous dilatation of the vessels occurs, followed by thrombosis and an impairment of the circulation. This stage is then followed by resolution, which more frequently terminates in necrosis with sloughing, hemorrhage and the formation of abscesses and cavities. In the extremely acute infection this process may extend over the whole lobe at nearly the same time, with death intervening before the gray stage is developed. This is represented by the true lobar types. The more slowly developing lesions occur not only in crops of different ages (*lésions en échelons*) but they have zones of different ages within the individual lesion from the center to the periphery as the lesions spread. There are usually all stages existing in the same patient and in the same lesion. The varying grades of chronicity then ensue with polymorphonuclears, and the gradual substitution of lymphocytes, plasma cells, fibroblasts, fibrous tissue and epithelialized cavities, as described before.

SUMMARY

The clinical course and the pathologic and bacteriologic observations of a fatal, chronic infection with Friedlander's bacillus are described. The micro-organism differed from that ordinarily described, in that it grew as well or better anaerobically as aerobically, it grew poorly on potato medium, it fermented lactose with acid and gas, and it produced coagulation in milk.

The pathologic condition was that of a subacute to chronic broncho-pneumonia with progressive necrosis and abscess formation exhibiting

a varied type of cell reaction that varied from lymphocytes, monocytes and plasma cells to focal abscesses of polymorphonuclears

Fibroblasts and connective tissue appeared about and within the older lesions, and the walls of the cavities became lined with metaplastic cuboidal or squamous epithelium. An important feature of the disease is the continuous succession of lesions, usually from the apex to the base of the lung, each of which passes through the same evolution and changes from the acute (described by Moisejew, Kokawa and others) to the chronic form already outlined.

The clinical aspects closely simulated chronic pulmonary tuberculosis, differing from it only in the general appearance of the patient, the irregularity in temperature and the obscure physical observations. The roentgen observations resemble those noted in chronic pulmonary tuberculosis.

STREPTOCOCCIC SEPTICEMIA WITH VASCULAR LESIONS

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AND

K. SEMSROTH, M.D.

PITTSBURGH

This report of a case of streptococcic septicemia, presenting an unusual clinical course and at autopsy showing a vascular lesion in several organs, merits careful consideration.

REPORT OF A CASE

History—A Negro, aged 32, entered the hospital with the sole complaint of pain in the lower portion of the back. He believed himself to have been in perfect health until three weeks before admission, when, while at work, he lifted some heavy metal and experienced a sudden, severe pain in the lower portion of the back. The persistence and radiation of the pain were characteristic of acute strain. The only additional symptom was nocturia two or three times, which the patient insisted had commenced subsequent to the injury.

The past history was unimportant except for several attacks of tonsillitis covering a period of years, gonorrhea eighteen years, and trauma to the right knee eight years, before the present examination. It is of considerable interest that this man did general work in a brass factory where, much of the time, he handled objects weighing 100 pounds (45.4 Kg.) or more without experiencing any symptoms.

Examination—Physical examination on admission to the hospital, three weeks after the onset of pain, showed persistent tenderness over both sacro-iliac joints and the lumbar muscles, which confirmed the obvious diagnosis of acute strain of the back. This condition responded promptly to orthopedic measures, and became entirely negligible within a few days.

Complete physical examination showed a very black Negro of excellent physique, sitting in bed without distress. He was mentally alert and cooperative. The temperature was 99 F., the pulse rate 90 and the rate of respiration, 20. The upper and lower teeth were much diseased and partially destroyed. The tonsils were moderately enlarged and, together with the pharynx, were swollen and diffusely injected. The left tonsil was covered with a thin, whitish exudate. A few small, nontender, cervical glands were palpated. The lungs were normal.

In the examination of the heart, the apex impulse was seen and felt in the fifth space inside the nipple line. A rub was felt over the lower part of the precordium to the left of the sternum. The left and right borders and the area of supracardiac dulness were not increased on percussion. At the apex, the first sound was loud, became accentuated and passed into a harsh systolic murmur.

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* From the Medical Service and Institute of Pathology of the Western Pennsylvania Hospital of Pittsburgh.

The weak second sound was followed by a definite pause and then later in the cycle by the appearance of a low-pitched diastolic murmur. At the base, the pulmonic second sound was greater than the aortic. A soft systolic but no diastolic murmur was heard. The precordial rub was audible in the area over which it was felt. The heart was rapid, at this time 120, but perfectly regular. The blood pressure was 118 systolic and 90 diastolic. Palpation of the abdomen was unsatisfactory owing to voluntary spasm, but, at a subsequent examination, the spleen was definitely felt. On the basis of these observations, a tentative diagnosis of rheumatic heart disease, pericarditis, mitral stenosis and questionably active endocarditis seemed justified.

The laboratory studies of the blood were consistent with the diagnosis of a rheumatic vascular process. The Wassermann reaction was negative. The red blood cells were 2,400,000 with 50 per cent hemoglobin, and the white blood cells were 6,300 with a differential count of polymorphonuclears, 78 per cent, lymphocytes, 14 per cent, transitionals, 6 per cent, and eosinophils, 2 per cent. The red cells showed moderate anisocytosis but no other feature. An essentially similar blood picture was obtained four days later, although the white count on this occasion was 9,000. *Streptococcus viridans* was readily cultivated from the blood stream. An electrocardiogram showed low potential in all leads especially I and III, the rate, 100, the rhythm, regular, P-R interval, 0.15, R diphasic in leads II and III, and high T complexes in leads II and III. The observations of the urine were, however, unexpected. Three examinations gave specific gravities of from 1.013 to 1.015, a heavy trace of albumin, from 10 to 35 red blood cells per high power field, from 3 to 12 white blood cells per high power field, and from 1 to 10 granular casts per low power field. Phenolsulphonphthalein dye was not eliminated in two hours and ten minutes on two tests made three days apart. The Mosenthal test showed marked fixation in the urine of both gravity and volume, with an increase of volume at night over that during the day. In five of the nine specimens, the specific gravity was 1.015, in three, 1.014, and in one of the specimens collected at night it was 1.012. These observations of the urine were supported by chemical analysis of the blood which gave nonprotein nitrogen, 162, creatinine, 88, and carbon dioxide-combining power, 32.

Course—The clinical course during the first two weeks of the patient's stay in the hospital of eighteen days proved uneventful. The patient was symptom-free and, since his back was better, insisted that he should be up and about. The clinical chart showed a maximum temperature of 100.4 F. on two occasions at the time of entrance, and no other observations above 99.8 F. in spite of a throat which was obviously inflamed for several days. The rate of the pulse varied from 106 to 86 during the first week and after that remained between 68 and 92. The blood pressure increased slightly from 118 systolic and 90 diastolic to 126 systolic and 94 diastolic. However, the daily cardiac examinations showed considerable variation in the location and intensity of the rub and of the murmurs.

The death of the patient was as rapid as it was unexpected. Four days before death, he complained of slight nocturnal dyspnea. Obvious dyspnea appeared only two days before death, but the patient remained alert and made no complaints although he was not as energetic as previously. The acute stage lasted less than eighteen hours. The dyspnea increased, he became irrational, and his great strength seemed to melt away. The pulse did not vary significantly, although the temperature became subnormal. The blood pressure rose slightly to a maximum of 136 systolic and 90 diastolic. As the coma increased respiratory distress was the predominant feature. The terminal picture was typical uremia.

Autopsy—Autopsy was performed four hours after death. As the interest centers chiefly around the heart and kidneys, a report of the detailed gross and microscopic examinations of these organs are given.

The heart showed moderate hypertrophy of the left ventricle. The subepicardial zone of the wall of the left ventricle showed a great many pale yellow or yellowish-white, firm patches, most of which were indistinctly circumscribed. Sclerosis of the mitral valve together with its chordae tendinae was present. Several groups of minute, pinkish-gray excrescences were present along the line of closure of the mitral valve with considerable hemorrhagic infiltration of the adjoining valvular substance. There were no gross lesions of the remaining valves.

On microscopic examination, the mitral valve was found to be the seat of a chronic productive inflammatory process with marked vascularization of the valvular substance. The latter contained groups of large mononuclear and, in places, syncytial cellular elements. These cells were hardly distinguishable from the cellular constituents of the typical Aschoff bodies which were present in the myocardium. However, their nodular arrangement was far less pronounced in the valve than in the muscle of the heart. Many of the smallest vessels of the valve showed an advanced stage of a chronic productive endovasculitis leading to partial obliteration of the lumen. Along the line of closure of the valve, numerous more or less focal subendothelial accumulations of mononuclear, presumably histiocytic, cells were seen. The centers of many of these accumulations of cells showed areas of necrosis, including the surface endothelium, although in many instances not covered by thrombi (fig 1). In the areas showing a more advanced stage of the active endocarditic process, the superficial valvular substance was partly replaced by broad bands of a homogeneous acidophilic material which blended imperceptibly into the adjoining deeper collagenous fibers (fig 2). In view of this behavior and of the fact that this homogeneous material did not extend into the overlying thrombi, but ended sharply in lines continuous with the adjoining endothelium, it appears reasonable to look on it as the result of a "fibrinoid" degeneration of the valve (Neumann¹) rather than as a penetrating thrombus in the sense of Ribbert.²

The myocardium was the seat of a moderate number of distinct, large, cellular nodules which, in many instances, showed the typical architecture of the Aschoff body. Here and there, foci of a similar cellular composition but lacking the distinctive nodular arrangement were found. These areas were most numerous in the subendocardial zone and in the vicinity of the medium-sized arterioles. The yellowish subepicardial patches, seen on gross examination, were found to correspond to areas of anemic necrosis of the muscular substance. The necrotic areas were composed of the supporting connective tissue, but with fragments of muscular substance and red blood cells scattered throughout. Evidences of an inflammatory nature of this process were lacking. Therefore, these areas might reasonably be interpreted as recent anemic infarcts such as are frequently seen in cases of coronary sclerosis. However, neither gross nor microscopic evidence of coronary sclerosis was found. On the other hand, numerous arterioles throughout the myocardium showed a lesion of predominantly alterative character. At intervals, subendothelial accumulations of a homogeneous, acidophilic substance

1 Neumann, E. Virchows Arch f path Anat **144** 201, 1896.

2 Ribbert, H., in Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1927, vol 2, p 216.

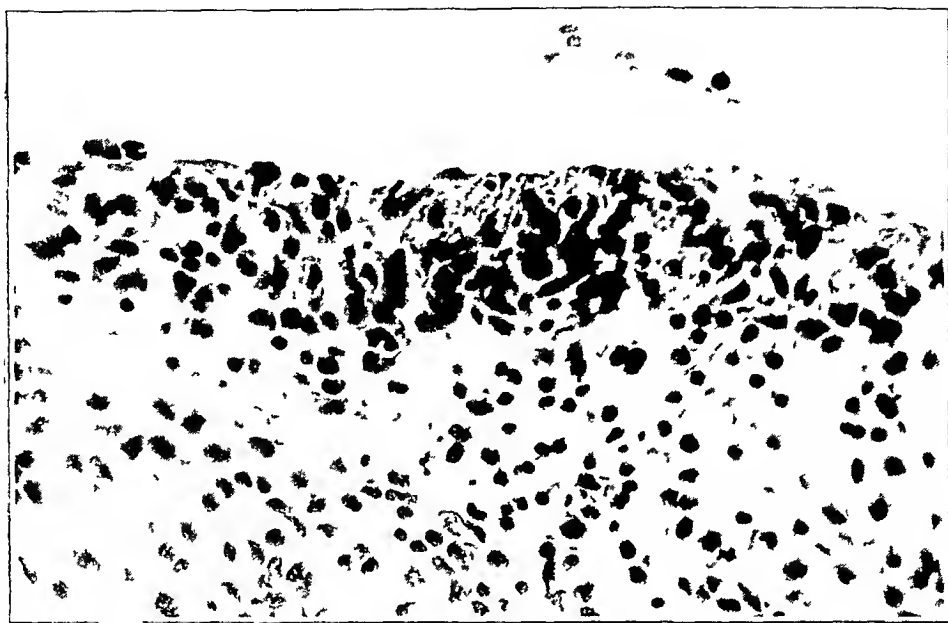


Fig 1—Mitral endocarditis with large cellular proliferative reaction and superficial necrobiosis, (Leitz 'Makam,' magnification $\times 320$)

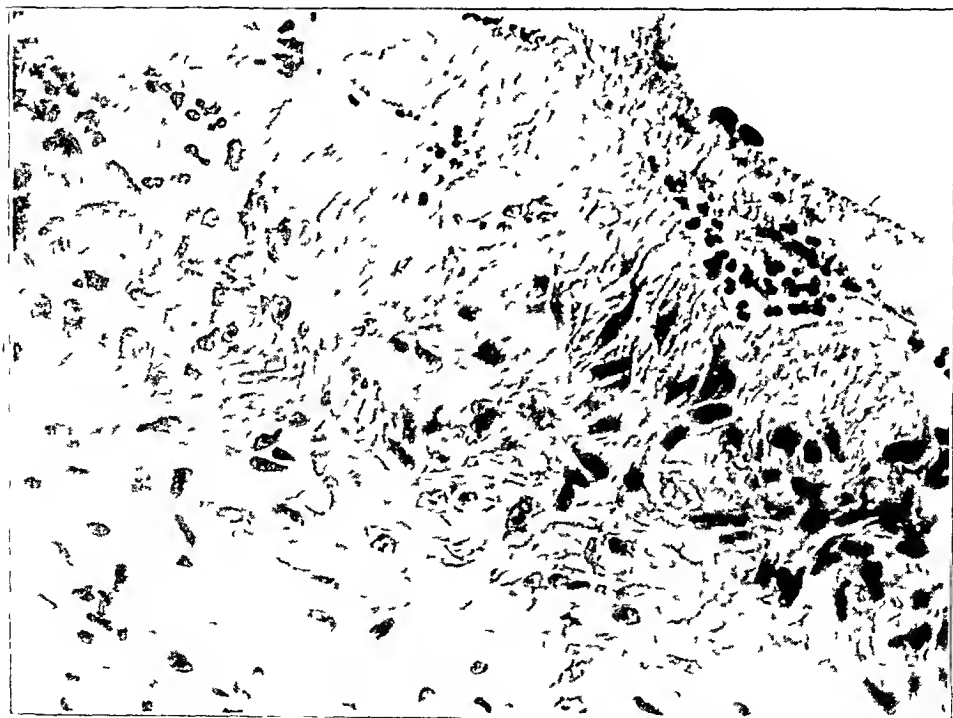


Fig 2—Mitral endocarditis with large cellular proliferation "fibrinoid" degeneration of the endocardial substance and thrombosis (Leitz "Makam," magnification $\times 320$)

protruded into the vascular lumen in a button-like manner. The appearance of this material closely resembled that of the homogeneous bands which were encountered in the advanced lesions of the endocardium (fig 2). In some of the larger arterioles, part of the media appeared to be replaced by this material. A moderate number of arterioles were practically obliterated by the subendothelial accumulation of this homogeneous substance in association with some proliferation of the endothelium (fig 3). Since coronary sclerosis was not present the anemic infarcts were considered to be the sequel to the foregoing alterative and obliterative arteriolar lesion.

On gross examination, the kidneys were normal in shape although considerably enlarged. The capsules stripped with difficulty. The surface and cut surface

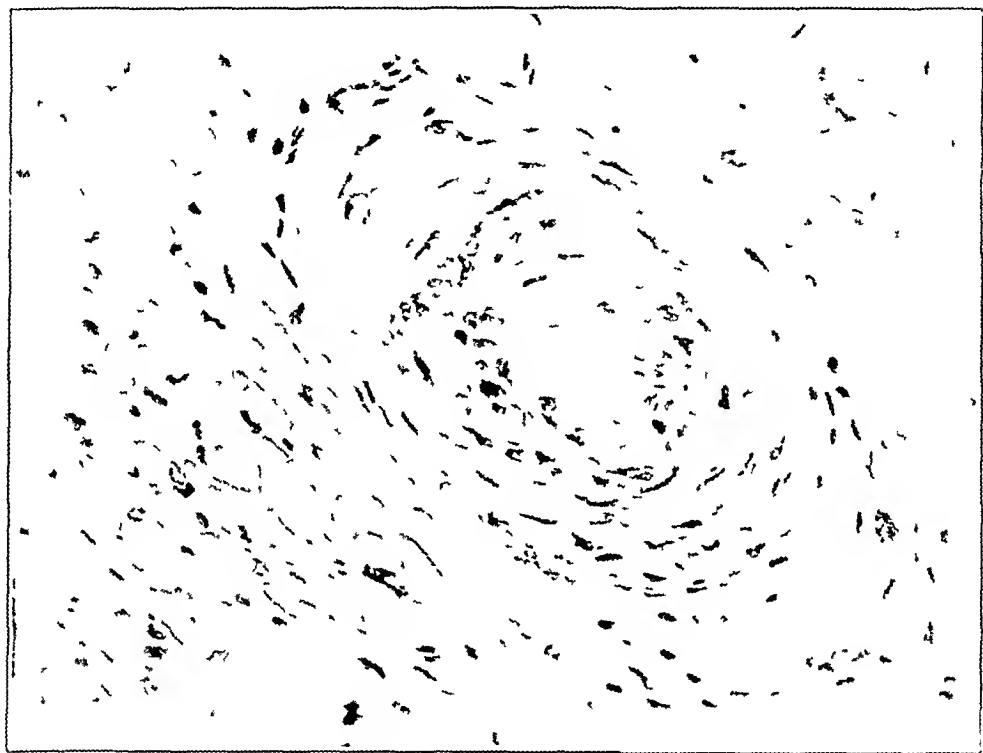


Fig 3—Alterative arteriolar lesion of the myocardium with homogenization of the inner layers of the vascular wall and partial obliteration of the lumen, (Leitz "Makam" magnification, $\times 320$)

were pale yellowish pink with innumerable, minute red dots. The normal architectural markings were distinct and the cortex relatively wide.

Microscopic sections of the kidney showed chronic degenerative changes of the cortical tubular epithelium. Hyaline casts were present in numerous tubules. A moderate increase in the interstitial connective tissue was apparent. Signs of a chronic glomerular lesion were practically absent. Evidences of an acute inflammatory lesion were found in many of the glomeruli such as necrosis of the glomerular tufts breaking down of the nuclei, accumulation of polymorphonuclear leukocytes. While the arteries appeared normal, most of the arterioles showed lesions that were closely analogous to those of the myocardial arterioles. Homogenization and necrobiosis of the inner layers of the vascular wall were frequently seen (figs 4 and 5). In many arterioles proliferative endarteritic processes were pronounced and led to a more or less complete obliteration of the vascular lumen.

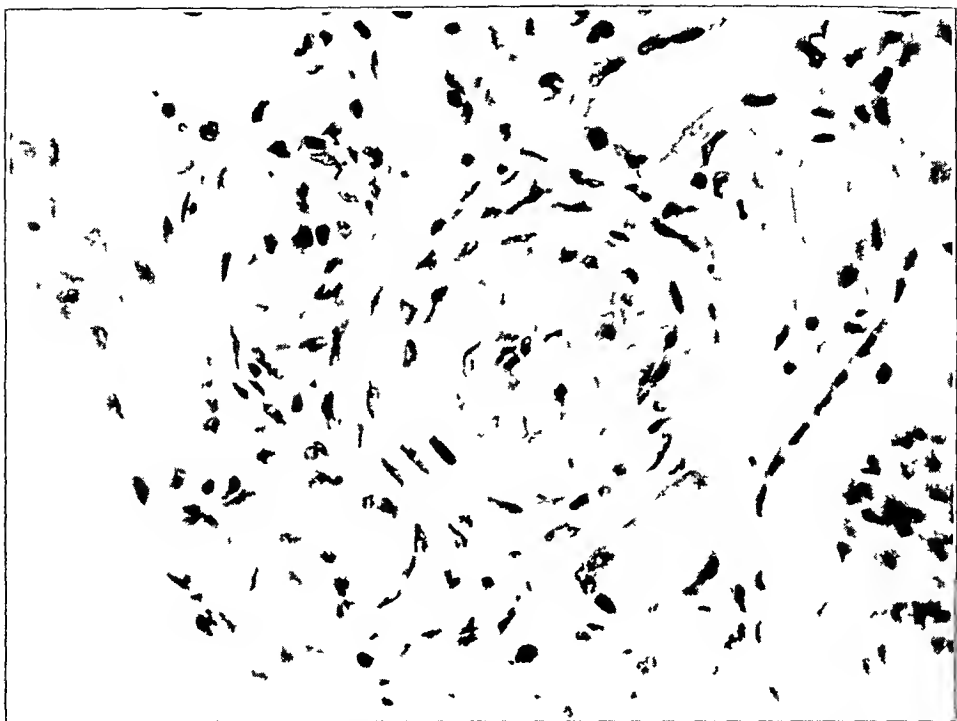


Fig 4—Alterative arteriolar lesion of the kidney. Note the ringlike homogenization of the inner layers of the vascular wall and the obliteration of the lumen (Leitz 'Makam,' magnification $\times 320$)

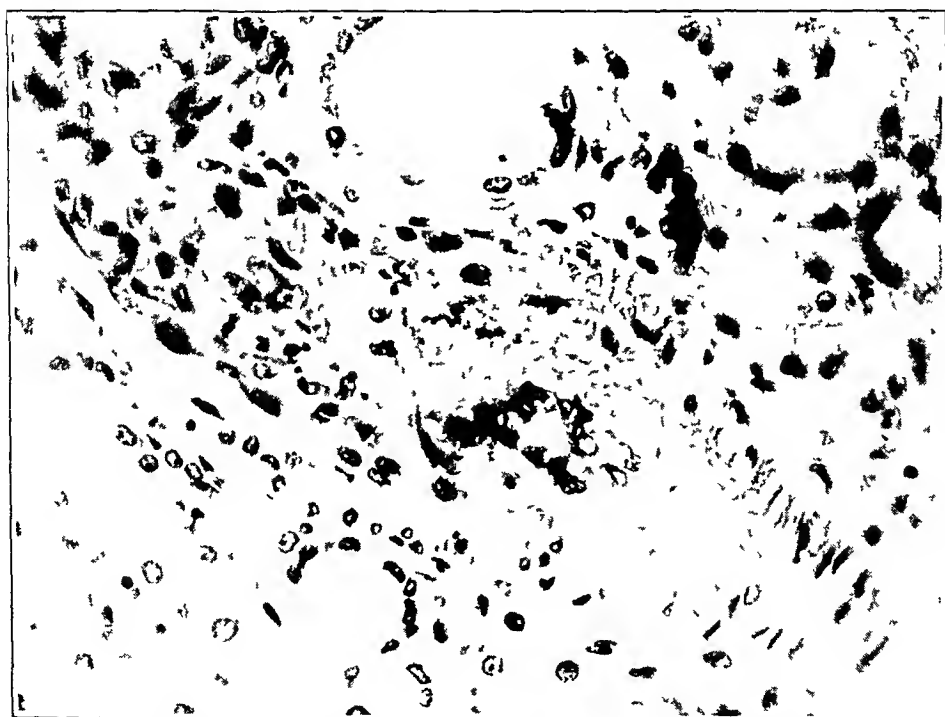


Fig 5—Arteriolar lesion of the kidney with homogenization and necrobiosis of the intima and subendothelial large cellular proliferation (Leitz 'Makam' magnification, $\times 320$)

The other postmortem observations that were of interest included ascites, extensive obliteration of the pericardial and pleural cavities by firm adhesions that were fibrinous in the pericardium but fibrous in the pleural cavities. There was moderate pulmonary edema. Early arteriosclerotic changes were noticed in the aorta. The spleen was moderately enlarged and firm. Chronic passive congestion of the liver and a striking intramural edema of the gallbladder were present. A culture of the blood of the heart taken at autopsy grew *Streptococcus viridans*, thus confirming the previous cultures.

COMMENT

From the anatomic point of view, the present case of sepsis due to *Streptococcus viridans* with rheumatic carditis is unusual. The pathologic observations in this case deviate from those found in the majority of such cases as both the myocardium and kidney show an alterative, productive and frequently obliterative arteriolitis. In the muscle of the heart, this arteriolar lesion resulted in the formation of areas of anemic necrosis. Alterative arteriolitis of the myocardium with subsequent necrosis of the vascular wall was referred to by Fahr³ as an occasional observation in "rheumatic disease." The infiltration of the vascular wall with fibrin, and the appearance of homogeneous masses and subsequent necrosis are the outstanding features of the "specific" lesion of the peripheral blood vessels described by von Glahn and Pappenheim⁴ in cases of rheumatic carditis. Although these authors found the typical vascular lesions in but ten of forty-seven cases, they regard them as specific, because, in their experience, the lesions are not found in any other disease. Even if the latter contention holds true, the nature of the vascular lesions cannot be wholly understood by regarding them as specific, because they are found only in the minority of the cases.

Siegmund,⁵ writing about the vascular lesions in chronic streptococcic sepsis (*Streptococcus viridans* sepsis), mentioned the occurrence of alterative arterial changes with necrosis of the wall of the vessel especially in the brain and kidneys. He was impressed by the close analogy existing between these lesions and the essential features of periarteritis nodosa. Not finding the changes in the majority of cases, he did not look on them as specific. Siegmund stated that similar vascular lesions may be induced in highly sensitized animals. He was, therefore, led to the conclusion that, in his cases of chronic streptococcic sepsis, alterative vascular lesions are the manifestation of a certain "state of immunity" which he designates as "hyperergic."

3 Fahr, T. Arch. f. Dermat. u. Syph. **130** 1, 1921.

4 von Glahn, W. C., and Pappenheim, A. M. Am. J. Path. **2** 235, 1926.

5 Siegmund, W. Centralbl. f. allg. Path. u. path. Anat. **35** 276, 1924.

Close morphologic analogies exist between periarteritis nodosa and the vascular lesions in the foregoing case of streptococcic sepsis. A recently observed case of periarteritis nodosa⁶ gave us occasion to compare those lesions with the vascular lesions that were described in the present case. In a number of instances, it was found that the early stages of periarteritis nodosa were not distinguishable from the lesions illustrated in figure 5. A further analogy between the process under consideration and periarteritis nodosa may be found in the relationship of invading micro-organism to the host. Low virulence of the invading organism is suggested by the course of the present case and, in the opinion of competent observers it is likewise an essential etiologic factor for periarteritis nodosa (Gruber⁷).

Evidence of the lack of specificity of this vascular lesion is also afforded by a recent case of chronic sepsis with a postmortem blood culture of *Streptococcus hemolyticus*. This patient gave no clinical or anatomic evidences of rheumatic disease, but did show vascular lesions of the kidney which were identical with those in the case now under discussion.

In view of the reported occurrence of this arteriolar lesion by others and of our own experience with it in cases of periarteritis nodosa and infection due to *Streptococcus hemolyticus*, the alternative arteriolitis which was found in the present case cannot be looked on as a specific lesion of rheumatic carditis. It appears rather that a relationship may exist between the development of vascular lesions of the type described and the degree of adaptation of the invading micro-organism to the host.

The clinical aspects of the case tend to support this conception of the relationship of organism to host. The fundamental disease was undoubtedly streptococcic sepsis, but of an intensity insufficient to elicit the usual signs of body reaction. The past history gives no clearcut story of previous streptococcic invasions. At the time of admission, an acute condition of the throat was noted although it was quite symptomless. It is worthy of emphasis that an insidious process of such magnitude could develop without a single warning symptom prior to a few days before death. Even an anemia of 2,500,000 cells with 50 per cent hemoglobin did not reduce the actual transportation of oxygen enough to produce symptoms. Again the absence of significant fever and leukocytosis in the presence of a positive blood culture of *Streptococcus viridans* is noteworthy.

6 Semsroth, K, and Koch, R. *Krankheitsforschung* 8 191 1930

7 Gruber, G. B. *Virchows Arch f path Anat* 258 441 1925

Anatomically the characteristic lesion of the disease occurred in the endothelial and subendothelial structures of the valves of the heart and small arteries of the myocardium and kidneys. The endocardium and the myocardium were grossly damaged. Although one may infer from the apparent activity of the disease process that much of the anatomic change developed in six weeks, it seems probable that the heart had been seriously injured for a much longer period. The electrocardiogram that was taken a week before death showed little in contrast to the advanced pathologic changes. Low potentials in leads I and II were the outstanding phenomena. The characteristic alteration of the R-S-T interval which is frequently associated with the localized myocardial degenerations of coronary disease was not found. This observation seems significant in view of the numerous areas of infarction that were apparently due to obstruction of the local blood supply. The observed physical signs were characteristic of an active disease of the rheumatic type involving the endocardium, myocardium and pericardium, but no features were noted that were diagnostic of the type of process that was present.

Likewise in the kidney, extreme vascular damage seemed to be the basis of the degeneration. Here again however, no basis was found for the prediction of the type of anatomic change from any of the available methods of clinical examination. The older anatomic changes were chiefly tubular and glomerular. Nephrosclerosis was conspicuously absent. These observations were scarcely to have been expected from the marked elevation of the nonprotein nitrogen and creatinine, the absence of edema, the fixed Mosenthal reaction and the negative phenol-sulphonphthalein reactions. These tests properly reflected the advanced degree of injury which the kidneys had sustained, but afforded no aid in the identification of the type of process responsible for the damage.

The clinical course in the later stages of the disease seemed to depend on the relative magnitude of involvement of the vessels of the different organs. Until within a few days of his death, the circulatory apparatus as a whole was functionally adequate. Likewise the kidneys had adequately handled the essential waste products of an unrestricted life and diet for an undetermined period. In this young man with both heart and kidneys structurally badly damaged, the functional renal insufficiency proved too great, and he died of uremia. In fact, it is probable that if he had been seen for the first time in the thirty-six hours before his death, an unhesitating diagnosis of 'chronic interstitial nephritis in the terminal stage' would have been made.

The point of view is therefore advanced that this case, on the basis of the anatomic and clinical evidence, was fundamentally one of low

grade sepsis in which the principal tissue reaction of the host is this unusual vascular lesion. The low virulence of the organism may be assumed to have permitted the development of the process for a prolonged period without the production of a typical host-tissue reaction to infection. The inevitable but latent symptomatology was therefore referred to the vital organs which failed secondarily to their local circulatory impairment. Such a process might be contrasted with "sub-acute bacterial endocarditis" which is also a streptococcal invasion, but with typical septic manifestations. In this disease the brevity of the course might preclude the development of the characteristic vascular lesions that were found in this case and, more especially, the secondary degeneration of the vital organs.

SUMMARY

An unusual case of sepsis due to *Streptococcus viridans*, with chronic and acute pancarditis and chronic and subacute nephritis is described.

A characteristic lesion that was found in the arterioles of both heart and kidneys is described at length. This lesion is regarded as causal to the secondary degeneration of both heart and kidneys.

The possible relationship of anatomic lesions and clinical course in a case of this type to low virulence of the invading organism and the absence of acute reaction on the part of the host is discussed and contrasted with more fulminating processes.

THE CLOSED INTESTINAL LOOP

II OBSERVATIONS ON DOGS WITH JEJUNAL AND ILEAL LOOPS AND CHEMICAL ANALYSES OF THE BLOOD*

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In a preceding paper¹ a method for making an accessible closed loop in the small intestine was reported. Observations were made on the relation of hydraulic pressure in loops of jejunum to the clinical condition of the animal. The prevention of intraloop pressure by aspiration of the fluid at intervals resulted in an uneventful recovery of the animal. Distention of the loop without aspiration brought about embarrassed circulation, followed by necrosis, rupture and death.

The present report is a continuation of that work including the making of loops in the ileum and a chemical analysis of the blood under the various clinical conditions that arose in this experimental procedure. Dogs were used throughout the experiments.

EXPERIMENTAL PROCEDURE

After entering the peritoneal cavity through a right rectus incision, a segment of ileum (or jejunum) was isolated with a suitable blood supply for making a loop from 10 to 12 cm. long. The jejunal loop was approximately 14 inches (32.53 cm.), and the ileal loop, 36 inches (91.44 cm.), below the ligament of Treitz. The ends were inverted and the continuity of the intestine reestablished by an aseptic, end-to-end anastomosis. The midline fatty appendage was then dissected back over the midline between the xiphoid process and the umbilicus, where the loop was attached by its antimesenteric border over a distance of 5 or 6 cm. with a fine silk suture which did not penetrate the submucosa. The loop thus lay between the incision and midline, with its level of attachment marked by a stitch.

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From the Department of Physiology, University of Oregon Medical School.

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1 Burget, G. E., Martzloff, K. H., Suckow, G. R., and Thornton, R. C. B. The Closed Intestinal Loop. I. Relation of Intraloop (Jejunum) Pressure to the Clinical Condition of the Animal, *Arch. Surg.* **21**: 829 (Nov.) 1930.

in the skin for convenience in locating it for tapping. Further details of this procedure will be found reported elsewhere.²

Forty-two animals were operated on as described. Eighteen of these died within the first two weeks from the following causes: two, pneumonia, three, snuffles, one, heima, and twelve, peritonitis. In the last group, loops of the duodenum were attempted in four animals, because of the parallel circulation with the intestine at this level, it seemed impossible to make a loop here which would be adequately nourished. The remaining twenty-four—fifteen of which had ileal and nine jejunal loops, lived in good condition for several weeks or months, and were serviceable animals in the laboratory.

All animals were given water forty-eight hours after operation and food after ninety-six hours. The temperatures were taken twice daily and frequent observations made of the general condition during the

TABLE 1—*Pressure Developed in Closed Loops of Ileum*

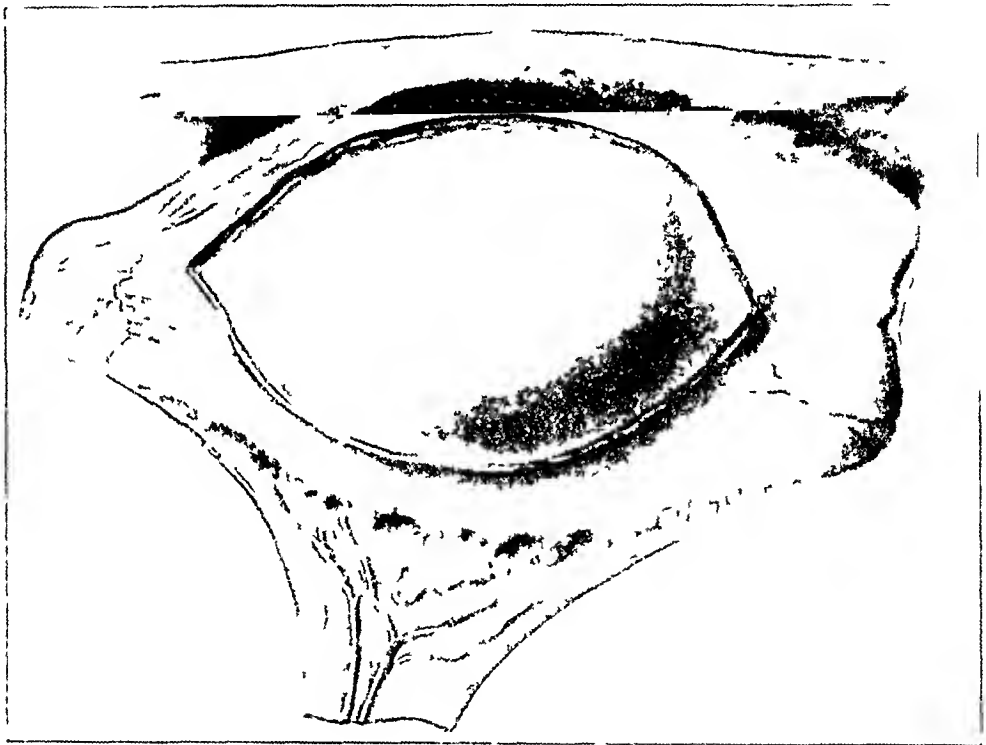
Dogs	Pressure Cm of Water	Quantity of Fluid With- drawn, Cc	Days Following Operation	Length of Life Following Operation
54	30	132	9	14 days
58	55	60	7	14 days, meningitis
61	58	165	14	Alive
67	40	125	9	Alive
68	42	75	4	139 days, killed
81	37	180	7	11 days
87	30	25	2	20 days
88	41	30	2	Alive

postoperative period. Little difference was seen in the clinical condition of animals with loops at different levels. The temperature seldom rose above 102° F unless infection was present in the incision or peritonitis developed. There was usually no vomiting, except when the loop became distended or peritonitis was present. The dogs were lively and eagerly took food and water. As a routine aspiration was done from eighteen to twenty-four hours after operation and as frequently thereafter as seemed advisable from the previous quantity of fluid withdrawn. The low loops needed aspiration less frequently than those of the jejunum, and as the loops became older, there was less tendency for the low ones to become distended with fluid. The hydraulic pressure in the loop was measured in a number of animals during the ten days following operation. Table 1 gives the highest pressures recorded in this period with the amounts of fluid withdrawn from eight ileal loops.

The average pressure in this series was 42 cm. of water, that found under similar conditions in jejunal loops was 39.5 cm.¹ These pressures

² Martzloff, K. H., and Burget, G. E. An Accessible Intra-Abdominal Closed Loop of Intestine Suitable for Physiologic Studies, to be published in a later issue.

are looked on as approximating a pressure that would be effective in blocking the circulation. When it is considered that these loops had recently been subjected to trauma and that increasing pressure over twenty-four or forty-eight hours had resulted in great distention with markedly stretched capillaries, it becomes plausible that this amount of pressure might be effective in materially embarrassing the circulation. A much higher pressure is required in an acute experiment on a normal segment of intestine.³ As indicated by the increased amount of fluid found in the loops of the ileum, there was greater distention in the ileum under an equal pressure than in the jejunum. There are probably two factors involved to account for this difference. These loops are slightly



Drawing of the loop of jejunum removed from dog 33 after thirteen months, with longitudinal incision showing putty-like material with which loop was filled

longer because of the wider branching of the mesenteric vessels of the ileum and the thinner musculature of the ileum allows it to stretch more under a given pressure.

The character of the fluid obtained at different times varies considerably. The first specimens following operation are of a dark blood color. After from eight to ten days there is no blood present and the fluid is dark gray, with considerable sediment. If the loop becomes markedly distended a large part of the fluid is quite clear with sediment

³ Dragstedt, C. A., Lang, V. G. and Millet, R. F. The Relative Effects of Distention on Different Portions of the Intestine. *Arch. Surg.* **18**: 2257 (June) 1929.

only in the last portion aspirated. On the contrary, loops that have not been disturbed for months tend to fill with a gray putty-like material, a chemical analysis of which has not been made. The accompanying illustration depicts such a loop taken from dog 33 after thirteen months. The dog was in good condition when it was killed. Grossly, the loop

TABLE 2—*Chemical Changes of the Blood in Dogs Following the Construction of a Jejunal Loop*

Dog	Hours After Operation											
	Normal			48			96			144		
	Non protein	Sodium	Carbon	Non protein	Sodium	Carbon	Non protein	Sodium	Carbon	Non protein	Sodium	Carbon
	Nitrogen	Chloride	Dioxide	Nitrogen	Chloride	Dioxide	Nitrogen	Chloride	Dioxide	Nitrogen	Chloride	Dioxide
52	30.0	362	47.0	32.0	462	38.1	35.0	412	62.7			
77	25.8	429	51.5	37.5	439	51.5	33.3	470	53.8	37.0	440	51.5
79	26.8	406	40.3	30.6	422	40.3	39.5	380	49.3	31.6	401	56.0
89	31.9	462	39.2	34.1	495	35.8	36.6	412	58.2	25.3	412	56.0
92	29.5	462	35.9	25.8	445	42.6	23.0	462	49.3	23.5	479	51.5
93	32.6	462	44.8	40.5	412	44.8	31.0	429	44.8	31.0	429	49.3
96	31.2	412	49.3	32.0	396	51.5	28.0	380	53.8	31.2	363	56.0
91	26.5	462	47.0	30.0	429	38.1	30.2	363	44.8	35.7	346	47.0

* In this and the following tables nonprotein nitrogen and sodium chloride are given in terms of milligrams per hundred cubic centimeters of blood and carbon dioxide is given in terms of alkali reserve figure.

TABLE 3—*Chemical Changes of the Blood in Dogs Following the Construction of an Ileal Loop*

Dog	Hours After Operation											
	Normal			48			96			144		
	Non protein	Sodium	Carbon	Non protein	Sodium	Carbon	Non protein	Sodium	Carbon	Non protein	Sodium	Carbon
	Nitrogen	Chloride	Dioxide	Nitrogen	Chloride	Dioxide	Nitrogen	Chloride	Dioxide	Nitrogen	Chloride	Dioxide
54	35.0	495	66.0		471	45.9	40.0	436	65.2	38.0	429	67.2
57	39.5	371	62.7	44.1	495	57.6	47.0	371	56.7	41.0	363	50.4
58	41.0	470	67.2	39.5	380	53.8	38.5	363	50.4	41.0	445	49.9
59	30.0	437	38.8	40.3	353	55.8	46.9	371	60.0	42.6	379	
60	36.6	462	50.4	30.7	437	43.7	36.6	412	47.0	33.3	404	49.3
61	35.7	445	40.3	37.5	356	44.8	26.8	462	45.0	24.0	471	41.9
68	31.0	412	44.8	29.4	396	42.6	44.0	363	45.9	48.4	376	45.2
84	30.0	492	53.8	45.0	447	33.6	42.6	429	47.0	39.5	419	56.7
88	36.2	389	51.5	39.5	445	44.8	33.8	445	51.5	16.9	396	54.9
91	31.9	445	49.3	39.5	462	47.0	46.9	478	44.8	35.7	445	47.0

appeared normal with an adequate circulation. A large part of this material consisted of epithelial cells and dead bacteria.

The flora found in the ileum was similar to that in the jejunum. *Bacillus coli*, *Bacillus welchii*, staphylococci and streptococci predominating. Although the p_H of the fluid in the loop varied between 5.8 and 8.8 this range did not seem to affect the nature of the flora. A separate report is being made on the bacteriologic observations.

That these loops function normally when kept in good condition that is, when they are not disturbed by distention and the formation of excess fluid and are kept washed out by the injection and withdrawal of a warm physiologic solution of sodium chloride, seems convincing from many experiments on digestion carried on by the injection of

TABLE 4—*Chemical Changes in the Blood in Two Dogs Without Operation But Given Routine Postoperative Care and Three Dogs with End-to-End Anastomosis but Without Construction of a Loop*

Dog	Hours After Operation											
	Normal			48			96			144		
	Non protein Nitro gen	Sodi um Chlo ride	Car bon Diox ide	Non protein Nitro gen	Sodi um Chlo ride	Car bon Diox ide	Non protein Nitro gen	Sodi um Chlo ride	Car bon Diox ide	Non protein Nitro gen	Sodi um Chlo ride	Car bon Diox ide
Normal I	39.5	445	40.3	51.7	412	42.6	44.1	429	42.6	38.0	445	49.3
Normal II	34.1	462	44.8	30.0	429	51.5	33.3	412	10.3	29.4	462	40.3
86	37.5	487	47.0	31.0	511	40.3	29.4	412	38.1			
94	39.5	429	42.7	35.7	429	51.5	30.6	445	44.8	39.5	596	47.0
95	34.9	445	49.3	35.4	462	44.8	25.4	495	10.3	31.9	429	44.8

TABLE 5—*Chemical Changes of the Blood in Dogs with Ruptured Loops and Peritonitis*

Dog 48					Dog 50				
Date	Non protein Nitrogen	Sodium Chlo ride	Carbon Dioxide	Comment	Date	Non protein Nitrogen	Sodium Chlo ride	Carbon Dioxide	Comment
10/19/29	41.9	454	51.2	Normal Operation	11/1/29	56.0	412	51.5	Normal Operation
19					2				
20	39.5	445	51.2		4	45.0	434	47.0	Vomited
21	50.0	379	49.2		5	47.0	433	47.0	Vomited
22	52.0	412	47.0		7	55.0	330	56.0	Dead
24	45.4	388	50.4		8				
26	48.5	375	61.6						
28	60.5	406	53.8						
29				Died					
Dog 78					Dog 63				
Date	Non protein Nitrogen	Sodium Chlo ride	Carbon Dioxide	Comment	Date	Non protein Nitrogen	Sodium Chlo ride	Carbon Dioxide	Comment
3/17/30	33.4	429	50.8	Normal Operation	2/1/30	46.9	406	47.0	Normal Operation
18					1				
20	57.7	429	42.5		3	50.2	379	47.0	
22	50.0	363	65.0		4	55.6	313	45.9	Vomited
23				Vomited	5				Dead
24	50.0	363	69.4						
26	46.3	330	72.8						
28	51.0	440	73.9						
4/1	57.7	280		Died					

substances into the loop and later by the withdrawal and washing out of the loop. The unabsorbed portion indicates indirectly how much of the injected substance has been taken up. In order to be certain on this point, many animals were killed for histologic examination of the loop. When the circulation is good and there has been no complication in the clinical recovery, microscopic examination of the mucosa reveals no changes that cannot be demonstrated in sections of normal intestine.

The use of such loops for experiments on digestion and absorption seems to us to have advantages over the other methods used

Since the closed loop has been used by different investigators to simulate intestinal obstruction, an analysis for chemical changes in the blood has been made as a matter of routine. Eleven cubic centimeters of blood were drawn from the left ventricle of the heart before operation and every forty-eight hours thereafter until recovery. Nonprotein nitrogen was determined by the method described by Koch and McMeekin,⁴ chlorides, according to Whitehorn⁵ and the carbon dioxide combining power after the Haskins-Osgood modification of the Van Slyke titration method.⁶ Table 2 gives the results in dogs with jejunal loops, and table 3, the results in those with ileal loops. In neither group is there any noteworthy change from the normal. As a further

TABLE 6—*Chemical Changes in the Blood Following Vomiting in Dogs with Old Loops*

Dog 32					Dog 49				
Date	Non protein Nitrogen	Sodium Chloride	Carbon Dioxide	Comment	Date	Non protein Nitrogen	Sodium Chloride	Carbon Dioxide	Comment
12/11/29	30.0	482	59.4	Normal	11/11/29	50.0	371	73.9	Vomited
5/20/30	24.4	421	60.5	Vomited	15				Vomited
7/16	28.8	365	60.5		16	62.5	330	78.4	
17	20.0	330	55.2		18	44.0	396	86.2	Vomited
					7/17/30	30.0	412	67.2	Normal

Dog 89				
Date	Non protein Nitrogen	Sodium Chloride	Carbon Dioxide	Comment
6/14/30	36.6	412	55.2	Normal
7/18				Vomited
14	36.0	412	49.3	
16	46.9	315	69.4	
17	40.0	300	73.9	
18				Recovered

comparison, in table 4 are given the observations in two normal dogs and in three dogs without loops in which end-to-end anastomosis had been performed. All received postoperative care as described for dogs with loops. The range of variation was as great as that in the foregoing groups. Table 5 shows the effect in four dogs with ruptured loops and peritonitis. The nonprotein nitrogen showed a moderate rise, especially on the day of death, and the chlorides fell, but not markedly. There was slight vomiting in each case except that of dog 48. The effect of distention in an old loop to the point of repeated vomiting but not

4 Koch, F. C., and McMeekin, T. L. A New Direct Nesslerization Micro-Kjeldahl Method and Modification of the Nessler-Folin Reagent for Ammonia, *J. Am. Chem. Soc.* **46** 2066 (Sept.) 1924

5 Whitehorn, J. C. A System of Blood Analysis, *J. Biol. Chem.* **45** 449 (Feb.) 1921

6 Haskins, H. D. and Osgood, E. E. Modification of Van Slyke's Method for Estimating the Alkali Reserve of the Blood, *J. Lab. & Clin. Med.* **6** 37, 1920

carried far enough to cause gangrenous areas with rupture is shown for dogs 32, 49 and 89 in table 6. There was a tendency toward a rise in nonprotein nitrogen and a fall in chlorides. The lack of marked changes in the blood would indicate that the vomiting was caused reflexly by distention of the loop. This is further brought out by the fact that these animals will take food almost at once following withdrawal of the fluid in the loop.

COMMENT

These observations indicate relatively unimportant changes in the chemistry of the blood in dogs with closed loops in which pressure in the loop is not permitted to bring on necrosis. There is no marked toxemia and no vomiting. Dragstedt⁷ observed that if distention is relieved by aspiration of the fluid in the loop, the toxemia is relieved and the blood chlorides tend to return to the normal level. While our results in dogs in which the loop was allowed to become distended show a moderate fall in blood chlorides, the toxemia was not great, as indicated by the fact that the animals would eat almost immediately following aspiration of the fluid in the loop. It would seem that vomiting accounts for the decrease in chlorides in these cases. Wangensteen and Waldron⁸ did not find a low level of blood chlorides in closed loops with gangrene when the continuity of the intestinal tract was reestablished. Further evidence on this point is shown in the dogs here reported with ruptured loops and peritonitis.

CONCLUSIONS

1 Dogs with closed intestinal loops (ileum and jejunum) have been kept alive for periods of from several months to more than a year by aspirating the loop and preventing overdistention.

2 After the first ten days, tapping becomes unnecessary except at infrequent intervals. The loops in the ileum are distended less frequently than those in the jejunum.

3 There is no difference in the clinical condition during recovery between animals with jejunal loops and those with loops in the ileum.

4 Closed loops in dogs that have made an uneventful recovery are normal histologically, physiologically, they digest and absorb food substances at a normal rate.

7 Dragstedt, T. R. Blood Chemistry in Intestinal Obstruction, *Proc. Soc. Exper. Biol. & Med.* **25**, 239, 1928.

8 Wangensteen, O. H., and Waldron, G. W. Studies in Intestinal Obstruction. IV. Strangulation Obstruction, A Comparison of the Toxicity of the Intestine and Other Tissues Autolyzed in Vivo and in Vitro. *Arch. Surg.* **17**, 430 (Sept.) 1928.

5 When absorption and secretion tend to remain balanced and the loop is not washed out, it gradually fills with a thick, gray, putty-like substance

6 The chemistry of the blood was practically normal throughout the uncomplicated recovery of these animals Distention of the loop accompanied by vomiting or rupture of the loop, with peritonitis and vomiting, causes some fall in the blood chlorides and a moderate rise in nonprotein nitrogen

CLEAR FLUID TEST MEALS (WATER, CAFFEINE SOLUTION, ALCOHOL) FOR USE IN FRACTIONAL GASTRIC ANALYSIS¹

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The merits of the fractional method of studying the gastric contents of the stomach have been conclusively established (Rehfuss¹). As a routine office procedure, however, I fully agree with the recent views so aptly expressed by Kaufmann² that a single specimen gastric test meal, carefully obtained and studied, fully suffices or may even be advantageous for general diagnostic purposes or as an index of gastric secretion and digestion. The fractional method should not replace, but supplement, the original single specimen gastric test. If one desires a more detailed study of the degree or curve of the acid wave, then there is no doubt that the extractions made at frequent intervals elicit more exact information. Every one is aware of instances in which the single extraction test meal did not reveal free hydrochloric acid, whereas the repeated extractions made in the same patient showed acids at one period or another. The relative advantages of these two methods have been fully and ably discussed, among others, by Hurst,³ Eggleston,⁴ Friedenwald, Gantt and Morrison,⁵ Friedenwald and Bryan,⁶ Hubbard and Lichty,⁷ and Rehfuss.⁸

When the fractional method was first introduced, the Ewald-Boas test meal, which had so successfully proved its merits in the single extraction method, was automatically adopted for the fractional method

¹ Submitted for publication, July 23, 1930

² Presented in preliminary form at the meeting of the American Gastro-Enterological Association, April 30, 1928

1 Rehfuss, M. E. *Am J M Sc* **147** 848, 1914, *Ann Clin Med* **2** 55, 1923

2 Kaufmann, J. *Arch f Verdauungskr (Boas Festschrift)* **43** 230, 1928

3 Hurst, A. F. *Lancet* **1** 111, 1923

4 Eggleston, E. L. *Gastric Secretory Disturbances*, *J A M A* **83**:260 (July 26) 1924

5 Friedenwald, J., Gantt, W. H., and Morrison. *Ann Clin Med* **2** 292, 1924

6 Friedenwald, J., and Bryan, W. J. *Presence of True Hydrochloric Acid in Gastric Contents in Carcinoma of the Stomach*, *J A M A* **83** 265 (July 26) 1924

7 Hubbard, R. S., and Lichty, J. A. *Ann Clin Med* **4** 393 (Nov) 1925

8 Rehfuss, M. E. *Ann Clin Med* **2** 55 (July) 1923

In some of the clinics abroad, however, I have observed the routine use of clear fluid test meals. The three test meals most frequently mentioned in the literature are caffeine solution, alcohol solution and plain water. In this study I should compare these with the Ewald-Boas test meal, as few detailed comparative statistics exist.

The test meals studied were: 1. The Ewald-Boas test meal: two slices of toast and a glass (240 cc) of weak tea. 2. The water test meal: 400 cc of ordinary tap water at room temperature. Distilled water and water at different temperatures were tried, but no outstanding differences were noted in the resulting gastric secretion. 3. The alcohol test meal: 300 cc of a 5 per cent pure alcohol solution. 4. The caffeine test meal: 400 cc of the following caffeine solution: caffeine purum 0.2 and water, 400 cc. All of these clear test meals were colored a faint blue by the addition of three drops of a 2 per cent solution of aqueous methylene blue (Katsch and Kalk⁹).

TECHNIC

The usual technic for fractional test meals was employed. The Einhorn duodenal tube was passed through the mouth into the stomach as soon as the patient awoke in the morning, any gastric contents possibly remaining in the fasting stomach were aspirated, and the respective test meal was given either by mouth or directly through the tube. Every fifteen minutes thereafter a 10 cc sample was aspirated, aspiration was repeated as long as the gastric contents persisted. The methylene blue (methylthionine chloride, U S P) stain was employed to indicate when the test meal had left the stomach. The contents gradually became a fainter blue the later they were aspirated, until finally a colorless liquid indicated that the test meal had entirely left the stomach. The subsequent contents aspirated were mainly of pure gastric secretion, aspiration was continued until no more secretion could be obtained. In this way some idea was gained as to the rapidity with which the contents left the stomach and the type of secretion remaining in the stomach after the test meal. Regurgitating bile or duodenal contents were at once evidenced by the change of the methylene blue to an easily recognizable, characteristic greenish hue.

MATERIAL FOR STUDY

Patients were selected from the general medical ward of the Lenox Hill Hospital and included persons with normal digestions as well as those with functional and organic lesions of the digestive tract.

On three successive days plain water, caffeine and Ewald test meals, were given to forty patients and the results were studied, respectively. An alcohol test meal was given on the fourth day to fifteen of the patients. The results of the plain water test meal given alone on three successive days were studied in three cases. Similar repeated experiments were made in three patients with the caffeine test meal alone, in three patients with the alcohol test meal alone and in three patients with the Ewald-Boas meal.

⁹ Katsch, G., and Kalk, H. *Klin Wchnschr* 4:2190 (Nov 12) 1925

RESULTS

Space does not permit the detailed publication of all the figures or charts obtained in these experiments but a general analysis is given in the accompanying table.

In 65 per cent (twenty-six cases) the four test meals gave almost identical results, i.e., the determinations for the free and total acids varied only within ten points (chart 1). In 35 per cent (fourteen cases) there were variations in the degree of acidity as high as twenty-five points, there was, however, no uniformity in these differences. Thus, of these patients, six (43 per cent) manifested the highest figures for acid secretion after the alcohol test meal, three (20 per cent), after the caffeine meal and two (14 per cent), following the Ewald test

Analysis of Forty Cases Studied by the Fractional Method, with the Ewald, Water, Caffeine and Alcohol Test Meals

	Number of Cases	Per Cent	Acid Figure	Free Hydro- chloric Acid	Total Acidity
Same results	16	62	High	From 50 to 80	From 80 to 110
	4	16	Normal	From 20 to 50	From 40 to 70
	3	11	Low	Below 20	Below 40
	3	11	Achylia		
Total	26	65			
Different results	3	20	High		
	4	29	Normal		
	5	35	Low		
	2	14	Achylia		
Total	14	35			
Highest figures	6	43	After alcohol meal		
	3	21	After caffeine meal		
	2	15	After Ewald meal		
	3	21	After water meal		

meal, while in three (20 per cent) the water meal appeared to be the most stimulating. It can therefore readily be seen that all types of differences were noted, but in general the alcohol meal was the most stimulating to secretion, while the other meals gave practically the same results.

The lack of agreement between the secretion stimulated by the various test meals was noted mainly in patients with gastric secretions of normal or lowered acid figures. In cases with high figures for acidity or complete anacidity the results were more uniform. Thus, in a group of twenty-six cases in which the determinations were the same, sixteen showed high figures for acidity (free hydrochloric acid from 50 to 80, total acid from 100 to 110), four, normal acidity (free hydrochloric acid from 20 to 50, total acid from 40 to 70), three subacidity (free hydrochloric acid below 20, total acid 40 or less) and three, achylia. Of the fourteen cases in which there were varying

results, three showed high figures for acidity, four, normal acidity, five subacidity, and two, achylia

The only outstanding discrepancy in the results of the tests occurred in two cases in which the fractional water test meal did not stimulate free hydrochloric acid on two and three different days, respectively, while the other test meals gave normal acid figures

When control experiments were performed in which patients received the same type of test meal on three successive days, just as many and as striking differences were noted in the degree of acidity on the

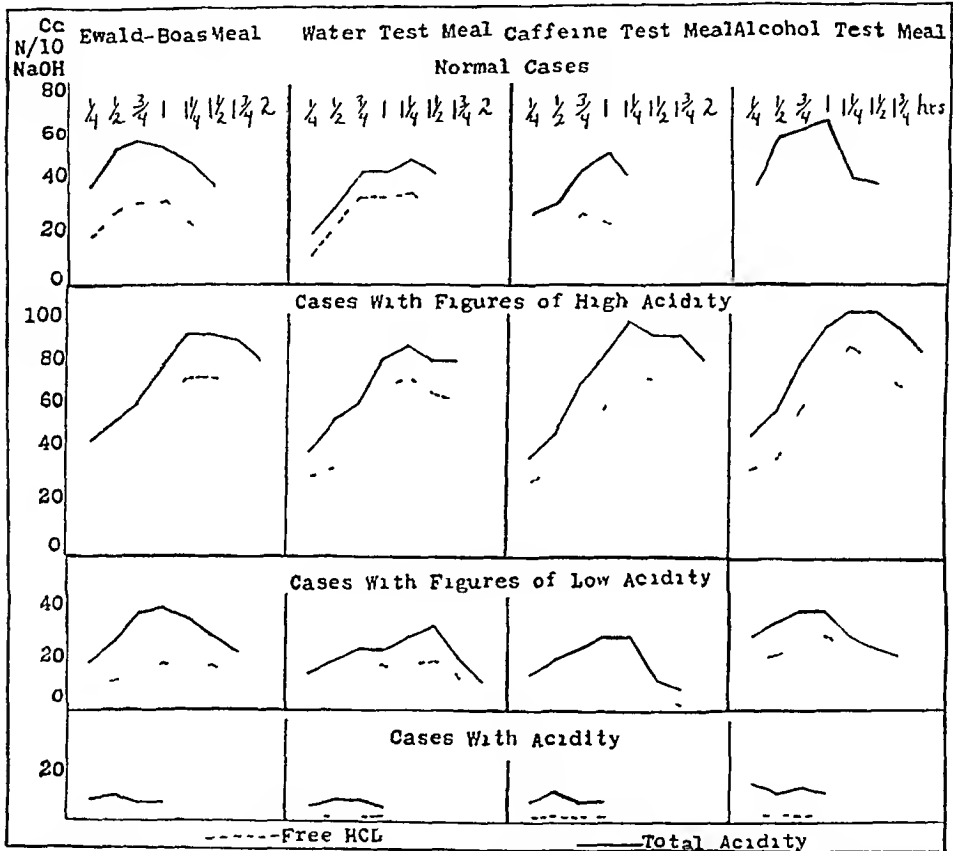


Chart 1—Comparative determinations after different types of test meals in which the results were practically the same

different days, after the same type of meal, irrespective of whether the meal was of tea and toast, water, caffeine or alcohol, as were evidenced after the different test meals (chart 2) This proved that the nature of the test meal was not the sole cause for the variability in the results It was found that duodenal regurgitation was a frequent factor in the variations both when different test meals were used and when the same type of meal was repeated The clear fluid test meals demonstrated this fact conclusively, as in these instances the slightest amount of regurgitated bile and the consequent immediate

lowering of the gastric acidity were at once noted. This diminished acidity might occur only in the contents of one extraction, the following specimen, extracted in fifteen minutes, showing normal acidity, or the regurgitation might persist and give a lowered acidity over a longer period of time. The blue color of the test meal would assume a characteristic greenish hue as soon as any form of alkaline duodenal con-

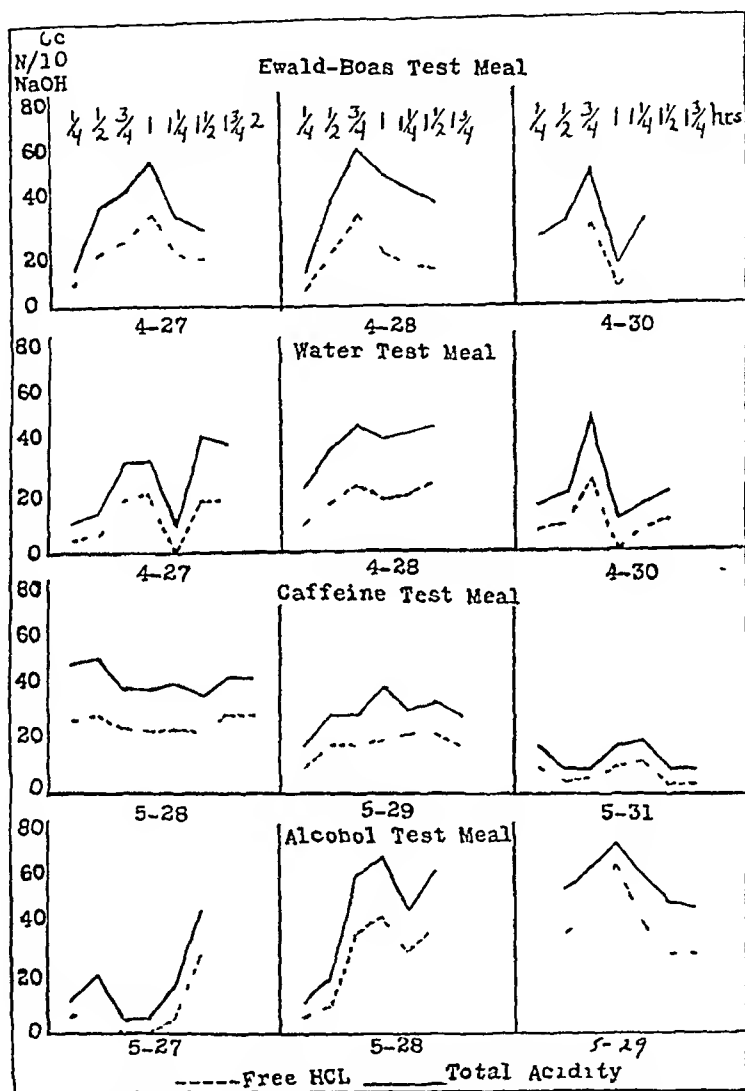


Chart 2—The same type of test meal repeated on successive days with striking differences in the results

tents would flow back into the stomach. The clear fluid test meals, which were uncolored by methylene blue, would show that regurgitation took place only if greenish or yellowish bile would regurgitate, but not if unpigmented intestinal contents would flow back. When one realizes that the intestinal contents are at least five times as alkaline as bile, the importance of the element of intestinal regurgitation becomes evident. It is more difficult to detect regurgitation with the Ewald meal, even

though stained with methylene blue, because of the brown color of the tea and toast, which interferes with the macroscopic detection by the change of color

Gaither¹⁰ too, has shown that one spurt of golden yellow bile may reduce the gastric acidity for a period of from ten to thirty minutes. Whether the reduction of acid is due to its neutralization by the intestinal contents or to true inhibition of the activity of the gastric glands is impossible to state. Macroscopic regurgitation occurred in our experiments in 7 per cent of the tests with the Ewald meal, in 11 per cent, with the caffeine meal, in 19 per cent, with the alcohol meal, and in 18 per cent, with the water meal.

While these figures show that regurgitation occurs twice as often with clear fluid meals as it does with the Ewald meal, it is possible that this greater frequency is apparent only because of the aforementioned difficulty in recognizing regurgitation with the tea and toast. This is particularly true if the regurgitation is slight and the consequent reduction of acidity results not in complete anacidity, but in a lowering of the acid figures.

WATER TEST MEAL

In the earliest studies of the gastric contents, von Leube (cited by Kaufmann²) employed water in the stimulation of gastric secretion. He used ice water and intended the coldness to be a factor in the stimulation of the acids. Water is well known to be a gastric stimulant (Heidenham,¹¹ Sanotski,¹² Pavlov,¹³ Foster and Lambert,¹⁴ Bergeim, Rehfuß and Hawk¹⁵ Sawitch and Zehony,¹⁶ Carlson, Orr and Brinkman¹⁷) Bergeim, Rehfuß and Hawk¹⁵ applied this knowledge practically in the form of a test meal consisting of 400 cc of water, and reported almost exactly the same acid curve with this test as with the Ewald meal. They felt that in the average normal person, water, either cold or warm, produced as great a stimulation as does the Ewald meal and can be substituted for it. Ivy¹⁸ also showed that 400 cc of water could be used for the determination of acids in the stomach,

10 Gaither E H Effects of Surgery of Stomach on its Subsequent Motor and Secretory Function, *J A M A* **91** 1079 (Oct 13) 1928

11 Heidenham *Arch f d ges Physiol* **19** 148, 1877

12 Sanotski *Arch d sc biol* **1** 589, 1892

13 Pavlov, I P The Work of Digestive Glands (trans by Thompson) ed 2, London, C Griffin & Company, 1910

14 Foster and Lambert *J Exper Med* **10** 820, 1908

15 Bergeim, O, Rehfuß, M E, and Hawk, P B *J Biol Chem* **29** 345, 1914

16 Sawitch and Zehony *Arch f d ges Physiol* **110** 123, 1913

17 Carlson, Orr, and Brinkman *Am J Physiol* **33** 91 1914

18 Ivy, A C *Am J Physiol* **46** 420 (July) 1918

but he did not feel that it could be substituted for the Ewald meal, as there is a marked variation in the response to stimulation by water in different persons. He met with several instances, as I have, in which secretion in the stomach was not stimulated by the ingestion of water. The stomachs that empty water slowly (150 cc or less in fifteen minutes) respond much more readily than those that empty water quickly. Moffatt, Mitchell and Powell¹⁹ found that some subjects show a complete achylia with water test meals, who give an acid curve of average height with a gruel meal. They objected to the water meal because of the difficulty in estimating the precise rate of emptying the stomach. This objection can be overcome, as I have shown, by the use of methylene blue.

The mechanism whereby water acts as a stimulant is not entirely agreed on and may, therefore, be due not to one but to several factors. Pavlov¹³ thought that the stimulation is chemical and due to the "prolonged and widespread contact" of the water with the gastric mucosa. This seems to be corroborated by the work of Foster and Lambert,¹⁴ who showed that the flow of gastric juice following the introduction of water is directly proportional to the volume of water employed, and by the work of Ivy,¹⁸ who found that the stomachs that are emptied of water slowly respond much more actively than those that are emptied quickly. He also noted a latent period of seven minutes for the human gastric glands when they were stimulated by water. Bergeim, Rehfuess and Hawk,¹⁵ however, were not able to demonstrate any latent period, and thus felt that a prolonged and widespread contact with the mucosa of the stomach was not necessarily a preliminary to stimulation in the human being, as Pavlov claimed to be necessary in dogs. Carlson, Orr and Binkman¹⁷ suggested that "water washed traces of gastric secretagogues into the intestines where they are absorbed and act on the gastric glands via the blood." It was also thought possible that the stimulating power of ordinary water was due to electrolytes contained in it, but comparative tests made with distilled water did not show striking or consistent differences, in fact, in one case, higher acid figures were obtained with the distilled water than with the tap water.

ALCOHOL TEST MEAL

The action of alcohol in various dilutions on the mucous membrane of the stomach has received a great deal of attention in the literature. The article by Kast²⁰ gives a splendid complete survey of the subject.

19 Moffatt, P. McG., Mitchell, G. O., and Powell, A. T. W. *Guy's Hosp Rep* **71** 1, 1921.

20 Kast, L. *Arch f Verdauungskr* **12** 486, 1906.

Kast (also quoted by Kelling²¹) showed that a solution of alcohol of less than 10 per cent is an excitant to gastric acids but not a stimulant to the superficial mucous membrane. It was not, however, until 1914 that Ehrmann²² suggested a 5 per cent alcohol solution as a gastric test meal (10 cc of absolute alcohol in 200 cc of water). He advised its use because it made a complete homogeneous solution, had no sediment or albumin, was sterile, could be easily sterilized for the study of gastric bacteria, was a strong gastric stimulant even when the patient had no appetite and could be extracted from the stomach through a small gastric tube. He employed it in the single extraction method and from one half to three quarters of an hour after its ingestion he was able to extract contents of almost pure gastric secretion.

Da Silva Mello²³ used an alcohol meal in the single extraction method (300 cc of a 5 per cent alcohol solution) in twenty-five patients. The acids were readily estimated, but he noted a regurgitation of bile in 90 per cent of the cases. As early as 1886, Gluzinski²⁴ had used a solution of alcohol of from 25 to 50 per cent for the express purpose of getting a reflow of bile into the stomach. The regurgitation of bile and duodenal contents was noted also by others (von Soos²⁵ and San Filippo²⁶) and became the outstanding objection to the use of the alcohol meal on account of the neutralization of the acids by the strongly alkaline duodenal contents. Grote²⁷ found that the alcohol meals gave figures for acidity that were about one-third lower than the degree of acidity after the Ewald-Boas test meals. Von Friedrich and Neumann²⁸ found regurgitation in 25 per cent of cases. Kotscham²⁹ found anacidity in thirty-three of seventy-two cases.

On the other hand, Kelling,³⁰ Wonckhaus³¹ and Vándorfy and Várady-Borbély³² employed the alcohol meal for the fractional analysis method, and were favorably impressed with its results. The latter

21 Kelling *Arch f Verdauungskr* **12** 491, 1906

22 Ehrmann *Berl klin Wchnschr* **51** 662, 1914

23 da Silva Mello *Berl klin Wchnschr* **53** 275, 1926

24 Gluzinski *Deutsches Arch f klin Med* **39** 405, 1886

25 von Soos *Orvosi hetil*, 1917, vol 61, no 1

26 San Filippo *Zentralbl f inn Med* **42** 382, 1921

27 Grote *Stomach Functional Test*, *Klin Wchnschr* **3** 792 (April 29) 1924

28 von Friedrich, L., and Neumann, K. E. *Deutsche med Wchnschr* **47** 43 (Jan 13) 1921

29 Kotscham *Cited in Klin Wchnschr*, July 16, 1925

30 Kelling *Arch f Verdauungskr* **24** 1, 1918

31 Wonckhaus *Deutsche med Wchnschr* **47** 43 (Jan 13) 1921

32 Vándorfy and Várady-Borbély *Ztschr f d ges exper Med* **50** 615, 1926

studied twenty-five patients in whom comparative tests with the plain water meal were made with practically identical results. In cases with high figures for acidity the water gave as good results as did the alcohol test meal. In cases of duodenal ulcer the water meal gave even higher figures. In cases with normal or subnormal figures for acidity, the water stimulation gave lower results than did the alcohol meal.

There seems to be no doubt that regurgitation is apparent less often with the Ewald meal than with the clear meals, and apparent more often with the alcohol than with the water meal. Because it is more readily recognized with the clear than with the Ewald meal, it can at once be considered as an explanation for a particularly low or absent acid secretion.

CAFFEINE TEST MEAL

Katsch and Kalk⁹ were the first to advise the use of a caffeine test meal. After trying various preparations and dilutions, they finally employed 0.2 Gm of caffeine purum in 300 cc of water. They realized the advantages of a clear fluid test meal free from albumin and salts, particularly in certain forms of examinations, but considered alcohol too irritating and nonphysiologic in its action. They compared the results in twenty-five patients tested with the alcohol and caffeine meals by the single extraction method and found the stimulating action of alcohol greater than that of caffeine. In two cases of borderline acid production, however, alcohol gave no secretion of free acid while caffeine did. They felt that the secretion following caffeine was not due to the direct irritation of the gastric mucosa, but to the stimulation of the acid-forming elements of the blood. A caffeine solution must not be confused with a solution of coffee, as the latter contains the additional products of roasting, among them probably histamine. Pincussohn,³³ however, showed that in dogs the caffeine solution produced no greater results than did the water in which the caffeine was dissolved. Goldbloom³⁴ too, inserted first a caffeine solution and then water into the large stomach of a dog with a Pavlov stomach, and watched the secretion in the small stomach. He found no difference between the caffeine and the water as far as the resulting secretions were concerned. Goldbloom carried out comparative tests with caffeine, water and alcohol by the single extraction method, and found that in 50 per cent of cases the caffeine gave little or no secretion after twenty or twenty-five minutes, while water showed secretion in 80 per cent of the cases and alcohol in almost 100 per cent.

33 Pincussohn, L. *Ztschr f Phys u diätet Therap* **11** 261, 1907

34 Goldbloom, A. A. *Arch f Verdauungskr* **42** 13 (Feb) 1928

COMMENT AND CONCLUSIONS

The Ewald-Boas tea and toast breakfast is undoubtedly the most practical test meal for the routine single extraction gastric analysis. Clear fluid test meals used in the single extraction method have as their great disadvantage the fact that they leave the stomach too rapidly, and that very often the stomach is empty after forty-five minutes. They can, however, be employed with advantage (Cheney³⁵) when one is especially desirous of studying the gastric cellular elements or food remnants, because they make a complete homogeneous solution and give no sediment. Furthermore, these clear test meals are free from albumin and salts, which is an essential in certain gastric tests, and in the study of bacteria they can be rendered sterile more readily. When the repeated extraction method of gastric analysis is employed instead of the single extraction method, these advantages of the clear fluid test meal hold true to even a greater extent. In addition, a gastric content of clear fluid can be extracted through the small duodenal tube more easily than can that of tea and toast, and the subsequent titration for the acids can be carried out without previous filtration of the numerous samples. The often quoted disadvantage of the clear fluid meals is that duodenal regurgitation occurs more often with them than with the Ewald meal, this, however, may be more apparent than real, and even if it does occur more frequently, it is readily recognized macroscopically and can be immediately taken into consideration. With the Ewald meal there is a risk that slight or moderate regurgitation may be entirely overlooked.

The clear fluid meals that have been employed are of plain water, an alcohol solution and a caffeine solution. The secretions following their ingestion have been compared with those after the meal of tea and toast. In 65 per cent of the cases the results of these three test meals are practically the same, so that any one can be employed in a fractional gastric analysis instead of the Ewald-Boas meal (chart 1). The differing results in the remaining 35 per cent of the cases need not necessarily be explained on the basis of the different constituents of the test meals, they can as well be attributed to the variations occurring in aliquot fractions obtained during a single analysis, and to the individual variations in a patient from day to day. The former factor has been definitely shown by the work of Kopeloff,³⁶ while the latter has been proved by myself in the series of experiments in which repeated examinations on three successive days showed widely varying results with the same type of test meal (chart 2).

35 Cheney, W. F. *Tr. Am. Gastro-Enterol. A.* 1928, p. 55.

36 Kopeloff, Nicholas. *Proc. Soc. Exper. Biol. & Med.* **19** 154, 1922, *Variations in Aliquot Fractions of Gastric Contents*, *Arch. Int. Med.* **30** 118 (July) 1922.

Of these clear fluid meals, alcohol is the most stimulating to gastric secretion, it is more stimulating than the Ewald-Boas meal. It has the disadvantage of producing in many patients, particularly in women who are unaccustomed to alcoholic drink, transient intoxicating effects. The scarcity of good alcohol in this country of prohibition is also a disadvantage.

The water meal is undoubtedly the simplest, it can be used any place or any time without preparation. It compares favorably with the other meals, in fact, the stimulating effect of the caffeine meal or the Ewald test meal may be due to the water element, as water is undoubtedly a strong gastric stimulant. However, there are occasional persons who do not secrete free hydrochloric acid in response to water, so that anacidity following a water meal must be controlled by an Ewald-Boas meal or by the use of histamine. The latter precaution has been adopted recently by many authorities when anacidity is found to follow any type of test meal.

EXPERIMENTAL AND CLINICAL STUDIES OF ERGOTAMINE

IV THE EFFECT OF ERGOTAMINE ON THE BASAL METABOLISM, CIRCULATION AND BLOOD SUGAR OF NORMAL PERSONS AND OF PATIENTS WITH THYROTOXICOSIS ¹

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Ergotamine and the closely related and pharmacologically similar ergotoxin constitute the principal alkaloids of ergot and exhibit all the effects of that drug on the uterus. In addition they have been shown to exert an effect on various parts of the sympathetic nervous system, in particular, a paralyzing or depressing action on the motor elements of that system that are stimulated by epinephrine. Briefly, in animals they not only antagonize the pressor effect of epinephrine on the systemic arteries, but under suitable conditions cause a reversal of the usual effect of epinephrine on the blood pressure.¹ Ergotamine inhibits the dilator effect of epinephrine on the coronaries,² and by its effect on the sympathetic nerves of the heart is said to slow the rate of sinus rhythm³ and to neutralize the accelerator action of epinephrine.⁴ In addition, ergotamine has been reported both to lower⁵ and to raise⁶ the blood

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1 Dale, H H On Some Physiological Actions of Ergot, *J Physiol* **34** 163, 1906

2 Rothlin E Ueber die pharmakologische und therapeutische Wirkung des Ergotamins auf den Sympathicus, *Klin Wchnschr* **4** 1437, 1925

3 Andrus, E C, and Martin, L E The Action of the Sympathetic upon the Excitatory Process in the Mammalian Heart, *J Exper Med* **95** 1017, 1927

4 Kolm, R, and Pick, C P Ueber die Bedeutung des Calciums für die Erregbarkeit der sympathischen Herznervenendigungen, *Arch f d ges Physiol* **189** 137, 1921

5 Lesser, E J, and Zipf K Ueber Herabsetzung des Blutzuckers beim normalen Kaninchen durch Ergotamin *Biochem Ztschr* **140** 612, 1923 Seidel, W Die Wirkung des Ergotamins (Gynergen) auf den Blutzuckerspiegel beim Kaninchen und beim Menschen, *Arch f exper Path u Pharmacol* **125** 269, 1927

6 Farrar, G C, Jr, and Duff A M, Jr Ergotamine Tartrate Its Direct Hyperglycemic Action and Its Influence on the Hyperglycemia Produced by Epinephrine in Normal Unanesthetized Dogs, *J Pharmacol & Exper Therap* **34** 197, 1928

sugar level during fasting, to diminish the hyperglycemic response to epinephrine⁷ and to lower the production of heat⁸. Certain writers, notably Rothlin,⁹ maintain that ergotamine also possesses a similar paralyzing action on certain of the inhibitory elements of the sympathetic system and is able, for example, to annul the inhibitory action of epinephrine on the small intestine. A more complete review of the literature dealing with experiments on animals is found in our previous publications¹⁰.

Because of these actions on the sympathetic system, ergotamine has become of considerable interest outside the field of obstetrics and has been used rather extensively in animal and clinical experiments in attempts to obtain direct or indirect evidence respecting the functions and behavior of the sympathetic nervous system. More recently it has been recommended as a therapeutic agent in conditions in which an overactivity of the sympathetic system exists, or is thought to exist, notably in cases of thyrotoxicosis.

However, as we have stated in preceding papers, the use of ergotamine for these purposes is based on evidence obtained for the most part from experiments on animals in which the doses employed and the conditions of the experiments were not such as are applicable to human subjects. Many of the clinical experiments purporting to show an action of ergotamine in man similar to that in animals have been poorly controlled. In other experiments it has simply been assumed that the action was the same. In view of these facts it was thought advisable, before carrying out certain projected experiments dealing with some of the functions of the sympathetic nervous system, to investigate certain effects of the drug. This has been done, trained normal dogs and normal persons being used as subjects, and the effect of ergotamine on the blood sugar, circulation and basal metabolism has been studied. Our

7 Michulicich, M. Ueber Glykosuriehemmung. II Ueber den Einfluss von Ergotamin auf die Adrenalin und Diuretinglykosurie, *Arch f exper Path u Pharmacol* **69** 133, 1912. Rothlin, E. Zur Pharmakologie des Blutzuckers, *Rev de pharmacol et de therap exper* **1** 103 (Sept) 1928.

8 Marine, D., Deutch, M., and Cipra, A. Effect of Ergotamine Tartrate on the Heat Production of Normal and Thyroidectomized Rabbits, *Proc Soc Exper Biol & Med* **24** 662, 1927.

9 Rothlin, E. The Specific Action of Ergot Alkaloids on the Sympathetic Nervous System, *J Pharmacol & Exper Therap* **36** 657 (Aug) 1929.

10 Youmans, J. B., and Trimble, W. H. Experimental and Clinical Studies of Ergotamine. I Effect of Ergotamine on the Blood Sugar and Epinephrine Hyperglycemia in Trained, Unanesthetized Dogs, *J Pharmacol & Exper Therap* **38** 121, 1930, II The Effect of Ergotamine on the Heart Rate of Trained, Unanesthetized Dogs, *ibid* **38** 133, 1930, III The Effect of Ergotamine on the Oxygen Consumption of Normal Trained Dogs, *ibid* **39** 201, 1930.

experiments on animals³ which have been reported elsewhere,¹⁰ have shown under these conditions results that have differed in some respects from those previously described. The present paper deals with the results obtained with normal human subjects together with observations made on a few patients, most of whom had thyrotoxicosis.

REVIEW OF THE LITERATURE

Effect of Ergotamine on the Metabolic Rate—Adlersberg and Porges,¹¹ who were the first to report the use of ergotamine in thyrotoxicosis,¹¹ merely stated that the metabolic rate was reduced. Since then a number of papers have dealt with the effect of this drug on the basal metabolism, but for the most part these have been reports of poorly controlled experiments, mostly on patients with thyroid disease observed during a course of long continued and often varied treatment. In most instances no experimental data are given. In their second paper,¹² Adlersberg and Porges reported a decrease of 7 per cent in the oxygen consumption of a patient with thyrotoxicosis within an hour after the subcutaneous injection of a single dose (0.25 mg). Under similar conditions Bouckaert and Noyons¹³ observed a lowering of from 2 to 29 per cent in the basal metabolic rate of eleven patients, and LaRoche, Camus and Labourdy¹⁴ a slight decrease (maximum 10 per cent) in five. Kerti,¹⁵ however, noted a rise of more than 5 per cent in three patients with thyrotoxicosis and no change in one, and Halder¹⁶ observed a slight rise in two patients from thirty to ninety minutes after the injection. Five cases are reported by Adlersberg and Porges¹² in which variable decreases in the basal metabolic rate were noted over periods of from days to months of treatment with ergotamine by mouth and subcutaneously. Halder¹⁶ obtained similar results, but concluded that they could not with certainty be ascribed to the effect of the ergotamine. We have been able to find but three papers describing the effect of the

11 Adlersberg, D., and Porges, O. *Wien klin Wchnschr* **37** 327, 1924.

12 Adlersberg, D., and Porges, O. *Ueber die Behandlung des Morbus Basedowii mit Ergotamin (Gynergen)*, *Klin Wchnschr* **4** 1489, 1925.

13 Bouckaert, J. P., and Noyons, A. K. *Diminution du métabolisme basal sous l'influence du tartrate d'ergotamine (gynergène) chez les basedowiens*, *Ann Soc scient de Bruxelles* **46** 320, 1926.

14 LaRoche, Camus and Lebourdy. *Le tartrate d'ergotamine chez les basedowiens et chez les hypersympathicotoniques*, *Rev franç d'endocrinol* **6** 52, 1928.

15 Kerti, F. *Die Einwirkung von Phlorrhizin und Gynergen auf den respiratorischen Stoffwechsel und ihre gegenseitige Beeinflussung*, *Wien klin Wchnschr* **41** 1119, 1928.

16 Halder, M. *Ueber den Einfluss des Ergotamins auf den Grundumsatz Basedowkranken*, *Schweiz med Wchnschr* **57** 411, 1927.

drug in normal subjects Kerti¹⁵ found a decrease in the metabolic rate in one experiment and no change in the others, while in one of Low and Krěma's¹⁷ normal subjects the rate fell from -8.9 to -16.2 per cent forty-five minutes after the injection of 0.5 mg of ergotamine. Halder studied the action of the drug in three normal subjects, and in these no effect was observed following the daily administration of from 3 to 6 mg by mouth for periods of from thirteen to twenty-nine days. It is evident from this review of the literature that previous studies fail to offer satisfactory evidence that ergotamine specifically lowers the production of heat in man.

The Effect of Ergotamine on the Pulse Rate—As in the case of the basal metabolic rate, many studies of the effect of ergotamine on the pulse rate consist of rather general observations made on patients during the course of continued treatment with the drug (either by mouth or subcutaneously), without adequate control of other factors that may have influenced the results. Thus a gradual decrease in the pulse rate was noted by Adlersberg and Porges,¹² Porges¹⁸ and Rutz¹⁹ in patients with thyrotoxicosis treated over periods of from six days to two or three weeks. A drop of from 10 to 40 beats per minute was observed by the latter author following the subcutaneous administration of from 0.25 to 0.5 mg three times daily for from six to ten days, but according to the author's tables the greatest slowing occurred shortly after the patients were placed in bed. Slowing of the pulse (maximum 21 beats per minute) in five of eight patients receiving the drug over periods of from ten to thirty days, with no effect in one and an increase in two, was reported by LaRoche, Camus and Lebourdy,¹⁴ who observed no correlation between the duration of treatment and the effect obtained. The effect of a single injection has been studied by Bouckaert and Noyons,¹³ who obtained a slowing of the pulse in five patients with thyrotoxicosis (maximum 26 beats per minute), no change in one and a slight increase in another, within an hour after the injection. Similar results were noted by LaRoche, Camus and Lebourdy,¹⁴ while Barath,²⁰ using intramuscular injections, saw only a slight slowing in the majority

17 Low, A., and Krěma, A. Grundumsatzstudien, Wien klin Wchnschr **41** 1453, 1928.

18 Porges, O. Umfrage über die Behandlung des Hyperthyreoidismus, Med Klin **23** 200, 1927.

19 Rutz, A. Ueber Vorbereitung und Nachbehandlung von Basedow Operationen mit Gynergen (Sandoz), Med Klin **22** 736, 1926.

20 Barath, E. Untersuchungen über die Ergotaminewirkung bei Menschen, mit besonderer Rücksicht auf seine klinische Anwendungsmöglichkeiten bei inneren Erkrankungen, Ztschr f klin Med **104** 713, 1926.

(from 8 to 12 beats per minute) and a more marked slowing (from 25 to 35 beats per minute) only in the patients who received the largest doses (0.5 mg) and who exhibited a severe reaction

More careful and better controlled studies of the effect of a single injection (intravenous) were made by Zorn²¹ and Wetterwald²². Both authors, using obstetric and gynecologic patients for subjects, obtained a marked slowing (average 40 beats per minute) following the intravenous injection of 0.5 mg. The slowing occurred within a few minutes after injection, the pulse rate returning to the preinjection level within two hours. In certain instances a coincidental slowing of the fetal pulse was observed by Zorn, who also was able to counteract the effect of ergotamine by the administration of calcium. Results similar to those of Zorn and Wetterwald were obtained by Kaufman and Kalk²³. In Immerwahr's²⁴ series of patients with various nervous disorders a slowing of from 14 to 22 beats per minute followed the subcutaneous injection of a similar amount. According to Immerwahr, the injection of atropine (1 mg) after the ergotamine caused first a slightly greater slowing of the pulse and then a moderate increase (18 beats per minute) in the pulse rate. In a series of 120 experiments on 50 subjects, Goldman²⁵ observed some slowing in all, the maximum being 60 beats per minute following the intravenous injection of 0.25 mg of the drug. During the period of nausea and vomiting induced by the drug, the pulse rate was increased. Atropine (amount ?) administered at the height of the effect of the ergotamine caused a greater slowing of the pulse. Goldman was unsuccessful in abolishing or reversing the effect of epinephrine on the pulse rate by the injection of ergotamine. Merke and Eisner²⁶ expressed the belief that the slowing caused by ergotamine is proportional to the rate of the pulse before injection.

Few studies have been made of the effect of ergotamine on the pulse rate of normal subjects under carefully controlled basal conditions

21 Zorn, W. Ueber die Wirkung von Gynergen auf Blutdruck und Puls beim Menschen, *Klin Wchnschr* **6** 204, 1927

22 Wetterwald, M. Ueber die intravenöse Darreichung des Gynergens (Ergotamin tartrat), *Schweiz med Wchnschr* **57** 292, 1927

23 Kaufman, F., and Kalk, H. Experimentelle Untersuchungen zur pharmakologischen Wirkung des Ergotamins, *Ztschr f d ges exper Med* **36** 344, 1923

24 Immerwahr, P. Ueber die Wirkung des Ergotamin auf Puls, Blutdruck und Blutzucker und ihre Beeinflussung durch Atropin, *Med Klin* **23** 1693 (Nov 4) 1927

25 Goldman, M., Jr. Recherches cliniques sur l'action de l'ergotamine sur le système végétatif, *Arch d mal du cœur* **21** 204, 1928

26 Merke, F., and Eisner, W. Der Einfluss des Ergotamins auf das Elektrokardiogramm beim Hyperthyreoidismus, *Deutsche Ztschr f Chir* **210** 239, 1928

Barath²⁰ and Goldman,²⁵ whose studies have been referred to did not distinguish between their results in normal subjects and those in patients. Halder¹⁶ was unable to obtain a slowing of the pulse in normal persons receiving the drug by mouth over long periods.

To summarize, ergotamine has been shown to cause a marked reduction in the pulse rate of patients when given intravenously in maximum doses. Smaller amounts and administration by the subcutaneous method cause a less marked slowing, while the evidence in favor of a significant effect of the drug when given by mouth to patients is unsatisfactory. Studies of its effect on the pulse rate of normal subjects under carefully controlled basal conditions have not been reported.

The Effect of Ergotamine on the Blood Pressure—The effect of ergotamine on the blood pressure of human subjects has been studied by several writers, most of whom have used patients as subjects. Barath,²⁰ who studied the effect both in patients and in normal subjects under basal conditions, but who did not distinguish clearly between his results in the two groups, found a variable effect depending on the initial level. In subjects with normal pressures there was usually a slight drop (from 10 to 15 mm systolic) often preceded by an initial rise of short duration, but in some subjects there was no change. Patients with hypertension showed the greatest lowering (from 30 to 35 mm systolic), with a slight rise in the diastolic pressure. On the contrary, Immei wahr,²⁴ in a series of patients, both those with normal endocrine and nervous systems and with various nervous and endocrine disorders, found a slight rise in the blood pressure in both normal subjects and those with hypertension, while in those with hypotension the pressure was slightly lowered, returning to the initial level in from thirty to sixty minutes. The injection of atropine (1 mg) was followed by a significant drop in about five minutes, even in persons whose pressure was elevated by the ergotamine. According to Zorn,²¹ the administration of 0.5 mg intravenously to obstetric and gynecological patients with a normal circulation and nervous system caused an increase of about 40 mm systolic which appeared in about forty minutes and disappeared in an hour or more. Increases in both systolic and diastolic pressures (from 20 to 60 mm) were noted by Kaufman and Kalk²³ following the intravenous injection of from 0.25 to 0.5 mg of ergotamine. Rutz¹⁹ noted a variable decrease in the blood pressure of eleven patients with thyrotoxicosis treated over a period of from six to ten days with from 0.125 to 0.25 mg of the drug subcutaneously, but did not control other factors that may influence the results. It is thus apparent that the reported effects of ergotamine on the blood pressure in man differ widely.

The Effect of Ergotamine on the Blood Sugar—Few studies have been made of the effect of ergotamine on the blood sugar level of fasting normal subjects. More often patients with various diseases have been used as subjects. Frequently ergotamine has been employed in experimental studies of the relation between the sympathetic nervous system and carbohydrate metabolism on the assumption that with ergotamine the action of the former could be abolished or modified. Seidel²⁷ observed a slight drop in the blood sugar of fasting normal men, but, according to Barath,²⁰ a more or less outspoken rise occurs in the majority, with no significant change in a few. Czezowska and Goertz²⁸ found an increase and Moretti²⁹ found no significant change under similar conditions. Immerwahr²⁴ obtained a biphasic response, a slight initial drop being followed by a small increase. The injection of atropine with the ergotamine made no difference in the response. In a group of patients, Goldman²⁵ obtained a drop in the majority, and Low and Krěma¹⁷ found a fall in two coincident with a decrease in the basal metabolism. In ten patients with diseases of the eyes Michail, Bendescu and Vancea³⁰ saw only a slight drop in three, each of whom had a rather high fasting level. Several writers reported a decrease in the blood sugar in diabetic persons following the injection of ergotamine (Seidel, Moretti and Goldman), and a similar effect was noted in patients with other diseases, particularly thyrotoxicosis (by the foregoing authors and by Rothschild and Jacobsohn³¹). On the other hand, Grunke³² found no effect in patients with various diseases, including diabetes, and Czezowska observed an increase in patients with exophthalmic goiter. Corbini³³ concluded that ergotamine has almost no effect on the hyper-

27 Seidel, W. Die Wirkung des Ergotamins (Gynergen) auf den Blutzuckerspiegel beim Kaninchen und beim Menschen, Arch f exper Path u Pharmacol **125** 269, 1927

28 Czezowska, Z., and Goertz, F. Influence de l'ergotamine sur le taux du sucre sanguin, Compt rend Soc de biol **98** 148, 1928

29 Moretti, H. L'action hypoglycemiant de l'ergotamine dans le diabete, Compt rend Soc de biol **97** 320, 1927, Glykamin und Ergotamin, Klin Wchn-schr **7** 407, 1928

30 Michail, D., Bendescu, T., and Vancea, P. Action de l'ergotamine sur le metabolisme basal et la glycemie dans les affections oculaires, Compt rend Soc de biol **98** 1468, 1928

31 Rothschild, F., and Jacobsohn, M. Die Wirkung von Ergotamin (Stoll) beim Basedow und im Tierversuch auf die Blutzusammensetzung, Ztschr f klin Med **105** 406, 1927

32 Grunke, W. Ueber den Mechanismus der alimentaren Hyperglykämie I. Mitteilung. Der Einfluss des vegetativen Nervensystems auf die alimentare Hyperglykämie, Ztschr f d ges exper Med **52** 488, 1926

33 Corbini, G. Azione dell'ergotamina sulla glicemia degli individui normali, epatici e diabetici, Policlinico (sez prat) **37** 85, 1930

glycemia in otherwise normal persons and in patients with hepatic disorders. In diabetic persons, it has a tendency to lower the blood sugar but the intensity of this action varies greatly in individual cases.

According to Loewenberg,³⁴ ergotamine depresses the alimentary hyperglycemia in normal subjects when small amounts of dextrose are used, and Czezowska²⁸ found that the alimentary hyperglycemia was diminished both in normal subjects and in those with diabetes. Moretti,⁹ however, was unable to obtain any effect on the alimentary hyperglycemia of normal subjects, although the increase in blood sugar after the injection of epinephrine was decreased (or prevented?) by ergotamine. A similar effect on hyperglycemia due to epinephrine was noted by Coelho and de Oliveira,³⁵ and depression of alimentary hyperglycemia in normal subjects or patients was found by Grunke,³² Hetenyi and Pogany,³⁶ and Rednik.³⁷ It is thus apparent that contrary results have been obtained in respect to the effect of ergotamine on the blood sugar of fasting normal subjects though there is general agreement that it lowers the blood sugar in persons with diabetes, and the majority of observers have noted a lessening of alimentary hyperglycemia in both normal subjects and patients.

EXPERIMENTAL DATA

The normal subjects were nine healthy, young adults accustomed to the procedures employed, which probably accounted for the low basal metabolic rates found in some of them. The following plan was generally followed. About six hours after a light breakfast, the subject was placed in a bed and allowed to rest quietly for at least an hour before beginning the experiment. Following the rest period there was a preliminary period of about thirty minutes during which the pulse and blood pressure were determined at frequent intervals, until a constant level was reached. At the end of this period the basal metabolism was determined, following which a sample of blood was drawn for the determination of blood sugar. After a short rest to allow the subject to recover from the slight disturbance caused by the metabolism test and venipuncture, 0.5 mg. of ergotamine (ergotamine tartrate, Sandoz) was injected subcutaneously. Repeated determinations of the basal metabolic rate, pulse rate, blood pressure and blood sugar were made over a subsequent period of three hours. Readings of the pulse rate and blood pressure were made at intervals of five minutes, during the first half hour and at intervals of from ten to twenty minutes during the subsequent

34 Loewenberg, R. D. *Pharmakologische Beitrage zur Frage der alimentaren Glykämie*, *Ztschr f d ges exper Med* **56** 147, 1927.

35 Coelho, E., and de Oliveira, J. C. *Influence de l'ergotamine sur l'hyperglycémie alimentaire chez les sujets normaux et chez les diabétiques*, *Compt rend Soc de biol* **99** 1527, 1928.

36 Hetenyi, S., and Pogany, J. *Ueber den Mechanismus der alimentaren Hyperglykämie*, *Klin Wchnschr* **7** 404, 1928.

37 Rednik, T. *Die Beeinflussung der Medikamente auf die Dextrose Belastungs Blutzuckerkurven als Leberfunktionsprüfung*, *Ztschr f klin Med* **109** 720 1928-1929.

period The metabolic rate was determined at hourly intervals, and the blood sugar was determined in some cases at intervals of thirty minutes, one, two and three hours after the injection of ergotamine In others the blood sugar was first determined at fifteen instead of thirty minutes after the injection and the three hourly periods omitted In additional experiments three of the subjects were given atropine (13 mg subcutaneously) before or after the injection of ergotamine, and its influence on the response to the latter was determined as already outlined In the experiments with atropine and ergotamine an attempt was made to time the injections so that the periods of maximum effect of the drugs, determined by control experiments, coincided Control experiments were performed with each subject, and the behavior of the metabolic rate, pulse rate, blood pressure and blood sugar, without the injection of ergotamine, was noted over a similar period of time In the case of the subjects in the experiments with atropine, control experiments were performed in which the effect of atropine alone on the pulse rate was observed

Three of the subjects were given 1 mg of ergotamine by mouth three times a day over a period of eight days, and the basal metabolic rate was determined every second day in the morning under standard basal conditions

Essentially the same plans were followed in the case of patients and, in some, similar control experiments were made In addition, several preliminary determinations of the basal metabolic rate alone were made to accustom the subject to the test

The majority of the determinations of the basal metabolism were made by means of a spirometer and an analysis of the expired air according to the method of Haldane In a few of the earlier experiments, a Roth-Benedict apparatus was used Subsequent experiments confirmed the results obtained with the latter method The pulse rate was counted with a stop watch, and whenever possible was counted for a full minute In no case were there irregularities of the heart beat (except slight sinus arrhythmia) which might have caused errors in the count The blood pressure was determined by the auscultatory method with a mercury sphygmomanometer Determinations of the blood sugar were made according to the method of Folin³⁸

In such experiments as these, the importance of slight stimuli and their effect on the pulse rate and blood pressure of subjects in a basal condition is often not sufficiently appreciated Even with trained subjects slight motion, anticipation of a painful injection, the entrance of persons into the room and similar disturbances are reflected in changes in these functions The effect on the metabolic rate (except at the time of testing) is less important In experiments in which readings of the pulse and blood pressure are made at frequent intervals, such changes may overshadow the effects of a drug, and it is necessary to allow for such temporary variations in accounting for the effect obtained

Certain features of the reaction to ergotamine, particularly the subjective symptoms, should be noted The injections themselves are painful, but curiously enough seem to be less painful to patients with thyro-

38 Folin, O Laboratory Manual of Biological Chemistry with Supplement, New York, D Appleton & Company, 1925, p 308

toxicosis than to the normal subjects, at least the patients complained less than did the latter. No other immediate ill effects were noted from the injections. Nausea was frequently experienced about thirty minutes after the injection, and vomiting occurred in one normal subject and in one of the patients. In some additional experiments, not reported here, in which ergotamine was given subcutaneously and dextrose by mouth to patients with thyrotoxicosis, vomiting invariably occurred. A dull headache was often noticed within an hour or so after the injection, and about two hours after the injection of ergotamine pain and soreness developed in the muscles. This soreness, which was particularly notice-

TABLE 1—*Effect of Ergotamine (0.5 Mg Subcutaneously) on the Basal Metabolic Rate of Normal Subjects*

Subject		Basal Rate Before Ergotamine, per Cent	Basal Metabolic Rate After Ergotamine		
			First Hour, per Cent	Second Hour, per Cent	Third Hour, per Cent
H F	Test	+12	-3	± 0	-2
	Control*	+5	-1	± 2	-9
J Y	Test	-19	-21	-19	-14
	Control	-23	-19	-24	-21
W T	Test	-1	-7	-8	-
	Control	-2	-1	-2	-5
F J	Test	-2	-5	+5	-
	Control	-1	+4	+7	+10
M T	Test	-1	-5	-10	-8
	Control	-7	-12	-10	-14
V B	Test	+3	+6	+5	+13
	Control	-	-	-	-
A C	Test	-2	-7	-6	+3
	Control	+3	-	-1	± 0
E J	Test	-14	-18	-7	-1
	Control	-11	-	-5	-6
M D	Test	+5	-3	-3	+2
	Control	-1	-	-3	-6

* Control experiments over the same period of time without ergotamine

able on walking, persisted and was frequently more severe the day after the experiment. Lassitude and a lack of energy were associated with this soreness, in the subjects who received the drug by mouth this effect was sufficient to cause an interference with their usual activities for two or three days after the drug had been taken. The patients with thyrotoxicosis seemed to suffer much less from the muscular soreness and the lassitude than did the normal subjects and rarely complained, though the normal subjects complained bitterly.

RESULTS

In none of the nine normal subjects was a significant effect on the basal metabolic rate noted during the three hours following the injection of the ergotamine (table 1). A slight increase (maximum 8 per

cent) occurred at the end of the third hour in three of the subjects and may probably be attributed to restlessness. In seven of the subjects, including the three in whom a rise occurred there was a variable drop (maximum 9 per cent) at some period after the injection, but in no case were the variations greater than those observed in the control experiments. In the case of the single subject (H F) in whom an apparently significant drop occurred, subsequent experiments indicated that the initial determination was not made under basal conditions. The injection of atropine before or after the ergotamine failed to influence the effect of the latter on the basal metabolism.

In all of the subjects the injection of ergotamine was followed by a slowing of the pulse, which was slight in some but probably definite

TABLE 2—*Effect of Ergotamine (0.5 Mg Subcutaneously) on the Pulse Rate and Blood Pressure of Normal Subjects**

Subject	Pulse Rate per Minute		Blood Pressure (Mm. of Mercury)			
	Before Ergota- mine	After Ergota- mine	Systolic		Diastolic	
			Before	After	Before	After
H F	80	74	122	124	72	82
J Y	76	54	98	100	72	78
W T	76	60	110	120	70	86
F J	90	78	104	106	66	68
M T	76	64	108	114	62	80
V B	64	58	112	122	70	88
A C	71	64	86	96	58	78
E J	69	63	96	112	56	90
M D	75	65	110	118	64	80

* The figures for pulse and blood pressure before the administration of ergotamine represent the last reading before giving the drug when these figures were consistent with the general basal level, otherwise the last basal reading. The figures for the pulse after the administration of ergotamine represent the lowest rate recorded, and for the blood pressure, the highest recorded, when apparently not due to the disturbing factors to which reference is made in the body of the paper. The control pulse rate in the case of subject T J is probably not basal.

in all (table 2). The maximum slowing was 22, the minimum, 6 beats per minute below the basal rate. This slowing of the pulse appeared most often about thirty minutes after the injection, and as a rule the rate gradually returned to normal by the end of three hours. In many of the experiments the slowing of the pulse was associated with the appearance of a respiratory sinus arrhythmia, and in the few instances in which this arrhythmia was present before injection it was increased during the period of bradycardia. In the experiments in which atropine was given before the ergotamine no effect of the latter on the pulse rate was noted, and the increase in pulse rate was as great as in the control experiments in which atropine alone was given. When atropine was given after the pulse had been slowed with ergotamine, the effect due to the latter was immediately abolished, and again the pulse became as rapid as it did with atropine alone (table 3).

The injection of ergotamine caused an increase in the blood pressure in nearly all of the experiments (table 2). The increase was greatest (maximum 34 mm) in the diastolic pressure and usually appeared about thirty minutes after the injection. A less striking (maximum 16 mm) and somewhat more variable response was noted in the case of the systolic pressure. These changes in the blood pressure persisted for some time, and the previous level was attained by gradual stages about three hours after the injection. In general the greatest effect on the blood pressure occurred in the subjects showing the greatest changes in the pulse rate, and it is interesting that these subjects were

TABLE 3—*Effect of Atropine on the Response of the Pulse Rate to Ergotamine in Normal Subject (H F), Comparison with Effect of Atropine Alone**

Atropine and Ergotamine	Time	Atropine
S4	2 00	74
S0	2 05	72
S2	2 10	72
S6	2 20	74
Ergotamine 0.5 mg	2 21	Atropine 1.3 mg
S1	2 25	80
S0	2 30	84
S6	2 35	92
Atropine 1.3 mg	2 36	
S8	2 40	92
S8	2 45	94
S8	2 50	94
S0	2 55	94
S4	3 00	94
S4	3 05	95
S4	3 10	95
S6	3 20	93
S6	3 30	93
S4	3 40	90
S0	3 50	85
S2	4 00	85
S0	4 10	82
S8	4 20	80
S4	4 30	80
S2	4 50	88
S6	5 10	78
S4	5 20	74

* In this table the experimental data have been adjusted to a common time basis

considered to have the most labile nervous systems. A typical protocol showing the effect on the pulse rate and the blood pressure is given in table 4. It should be noted that temporary variations, due to the causes mentioned, tended to obscure the effect of the drug, particularly in the cases in which the effects of the drug were slight. In two of the subjects, the injection of both atropine and ergotamine resulted in a greater rise in blood pressure, both systolic and diastolic, than when ergotamine alone was used.

Ergotamine had no significant effect on the blood sugar level in these experiments, and the slight variations above and below the initial level were no greater than occurred in the control experiments and are believed to lie within the range of normal variation (table 5).

At some time after the injection, all of the subjects showed an increase over the initial value (maximum 10 mg per hundred cubic centimeters), and in seven subjects there was also a fall (maximum 8 mg)

TABLE 4—*Effect of Ergotamine on the Pulse Rate and Blood Pressure in a Normal Subject (M D)*

Time	Pulse Rate Beats per Minute	Blood Pressure (Mm of Mercury)		Comment
		Systolic	Diastolic	
1 14	76	106	60	
1 20	75	106	64	
1 22	78	110	66	
1 25	76	108	66	
1 28	76	112	68	
1 30	76	110	64	
1 31				Metabolism test
1 40	78			
1 50	75	118	74	
2 00				Electrocardiogram
2 03		108	76	Venipuncture
2 09	Ergotamine 0.5 mg subcutaneously			
2 12	72	108	70	
2 15	69	110	70	
2 20	69	106	60	
2 25	69	108	70	
2 30	70	114	74	Feels "queer"
2 35	65	110	70	
2 40	68	110	74	Venipuncture
2 45	69	118	80	
2 50	69	118	80	
2 55	65	116	70	
3 00		118	76	Metabolism test
3 12				Venipuncture
3 20				Electrocardiogram
3 23		100	64	
3 30	76	112	66	
3 40	67	112	68	
3 50	69	110	72	Pain in muscles
4 00	69	114	72	
4 01				Metabolism test
4 09				Venipuncture
4 10	68	116	70	
4 25	70	112	64	
4 40	70	114	74	
5 05	70	110	74	Metabolism test
5 10	78	108	68	

TABLE 5—*Effect of Ergotamine (0.5 Mg Subcutaneously) on the Fasting Blood Sugar Level of Normal Subjects*

Subject	Before Ergotamine	Blood Sugar (Mg per 100 Cc) After Ergotamine				
		15 Minutes	30 Minutes	60 Minutes	120 Minutes	180 Minutes
H F	73	69	73	73	82	
J Y	93	91	99	90	93	
W T	76	76	76	76	83	
F J	64	64	63	68	65	
M T	74	74	66	83	77	
V B	85		86	86	88	84
A C	87		87	91	91	95
E J	77		76	81	75	78
M D	66		69	64	66	

No change in the basal metabolic rate occurred in any of the three subjects who were given ergotamine by mouth (table 6). It was noted, however, that the respiratory quotients showed a tendency to drop toward the end of the experiment.

In general, the effect of ergotamine on the basal metabolic rate of patients with thyrotoxicosis was similar to that seen in the normal subjects (table 6). The effect on the pulse rate, however, was more marked, and greater changes were seen more often. In no case did the drug fail to cause a definite increase in the diastolic pressure, and the effect on the systolic pressure was much more marked than in the normal subjects (table 7). In two subjects (J B and N R) in whom the diagnosis of thyrotoxicosis was doubtful, the changes in pulse rate

TABLE 6—*Effect of Ergotamine (0.5 Mg Subcutaneously) on the Basal Metabolic Rate of Patients with Thyrotoxicosis*

Subject	Basal Metabolic Rate Before Ergotamine, per Cent	Basal Metabolic Rate After Ergotamine		
		First Hour, per Cent	Second Hour, per Cent	Third Hour, per Cent
J B	+ 2	± 0	+ 2	
I C	+22	+26	+14	+22
N R	+ 8	- 2	+ 4	+ 7
D C	+79	+87	+81	+80
M G	+54	+50	+57	+65
E P	+79	+94	+83	+94
J B	+10	+16	+19	+20
O H	+54	+63	+70	+75

TABLE 7—*Effect of Ergotamine (0.5 Mg Subcutaneously) on the Pulse Rate and Blood Pressure in Patients with Thyrotoxicosis**

Subject	Pulse Rate per Minute		Blood Pressure (Mm. of Mercury)			
			Systolic		Diastolic	
	Before Ergotamine	After Ergotamine	Before Ergotamine	After Ergotamine	Before Ergotamine	After Ergotamine
J B	76	70	110	112	74	80
I C	78	63	116	162	58	90
N R	108	93	116	120	70	76
D C	122	105	150	174	70	94
M G	100	84	140	160	80	90
E R	104	101	132	172	64	86
J B	65	56	118	148	64	80
O H	96	82	142	174	64	104

* See note under table 2

and blood pressure were about as great as those in normal subjects. In four of the six patients with definite thyrotoxicosis the injection of ergotamine had no significant effect on the metabolic rate. Minor variations both above and below the initial determination occurred at some time during the experiment (maximum 11 per cent and 8 per cent, respectively). In one patient (E R), with an initial rate of +79 per cent, the rate rose in the first hour to +94 per cent, fell to +83 per cent at the second hour and again rose to 94 per cent at the end of the third hour. In another patient (O H), with an initial rate of +54 per cent, the

rate rose steadily to $+75$ per cent by the end of the third hour. Of the two patients in whom the diagnosis was uncertain, a drop of 10 per cent occurred in one (N R) within the first hour and no change in the other. It is interesting to note that of the six patients with thyrotoxicosis a rise of greater or less degree, at some time after the injection of the drug, was noted in all. The respiratory quotients showed changes which followed the variations in the metabolic rate. Two patients (I C and D C) were given 0.25 and 0.125 mg of ergotamine, respectively, subcutaneously, three times daily, for a period of from six to eight days. At the end of this period the basal metabolic rate remained unchanged in the first patient and had dropped from $+76$ to $+63$ per cent in the other, but during this time the patients were at rest in bed, under general medical treatment, and the lowered rate in the second patient may well be attributed to this nonspecific therapy.

In the case of two of the patients, determinations of the blood sugar were made as in the normal subjects. In one instance (I C) the blood sugar fell from 135 to 81 mg per hundred cubic centimeters at the end of an hour, and in the other (D C) from 82 to 71 mg in two hours.

COMMENT

From our experiments it seems apparent that ergotamine has little, if any, direct influence on the production of heat in normal subjects under basal conditions. This observation, which is in accord with the results obtained by us with trained, unanesthetized dogs, is the more significant in view of the numerous reports that ergotamine lowers the production of heat in both animals and man. It should be emphasized, however, that in the past few experiments have been performed with normal subjects under strict basal conditions. The majority of studies have been made with patients rather than normal persons as subjects. In either case the experimental data reported are generally incomplete, but a careful examination of the data given suggests that the supposed effect of the drug has been largely illusory and that failure to secure proper basal conditions or to evaluate and control properly other factors concerned has been responsible for the apparent effect of the drug. Nevertheless, the failure of ergotamine to influence the production of heat in normal subjects is not proof that in patients with certain abnormal conditions the drug is ineffective. Our results with patients, while strongly suggestive, are inconclusive in this respect.

The view is generally held among those who have reported a lowering of heat production by ergotamine that this result is accomplished by a paralyzing or depressant action on the sympathetic nervous system. Such an explanation might serve to explain the difference in our results

from those of others on the assumption that the abnormal activity of the sympathetic system assumed to be present in certain diseases and particularly in patients with thyrotoxicosis, made the sympathetic system more sensitive to the action of the drug. This explanation, while it receives little support from our clinical studies, cannot be dismissed and will be discussed further. There exists, however, another explanation that may serve to explain the reduction in the basal metabolic rate which is sometimes seen following the administration of ergotamine. Reference has already been made to the lassitude and feeling of fatigue which follow the administration of the drug, especially when it is administered over a period of several days. As a result of this, greater relaxation may be secured, particularly in patients subject to overstimulation, and with it a more nearly basal condition. In other words, although ergotamine may not possess a direct action on the production of heat, by indirect means it may permit a determination more nearly basal. A similar explanation has been offered by Merke³⁹. Such an effect would of necessity vary considerably with individual subjects and is therefore in accord with the marked individual variations in response to the drug.

The failure of ergotamine to affect the fasting blood sugar level of normal subjects, again in accord with our results in trained unanesthetized dogs, is important because the reported effects on the blood sugar have also been ascribed to an action on the sympathetic nervous system. This failure to affect the blood sugar of fasting normal subjects agrees with the results of several other workers, and it seems safe to conclude that under basal conditions ergotamine is ineffective in this respect in these persons. It must again be emphasized that this conclusion applies only to fasting normal subjects, since the work of other investigators apparently shows a definite influence of ergotamine on the changes in the blood sugar in response to certain stimuli, such as the administration of epinephrine, and in patients with certain diseases. Unreported experiments of our own suggest a similar effect. This failure of ergotamine to modify the sympathetic nervous system under basal conditions and to affect it under conditions that may stimulate it is of considerable interest and will be discussed further.

The most marked effect of ergotamine was on the pulse rate and blood pressure. Similar, but greater, effects on the pulse were obtained by us on trained, unanesthetized dogs, and a number of writers have obtained results similar to ours in man, although in many instances the

39 Merke, F. Ueber die Wirkung des Gynergens beim Morbus Basedowi, Schweiz med Wchnschr 57:833, 1927

reported reduction in pulse rate has undoubtedly been due to factors other than the drug. This slowing of the pulse has most often been explained as a paralyzing or depressing action of ergotamine on the accelerator nerves of the heart. From the results of our experiments, both with animals and with man, we are unable to agree to this explanation. Rather, the slowing appears to us to be due to a vagus stimulation or sensitization. We do not mean by this a relative stimulation due to partial release of accelerator control, as suggested by LaRoche, Camus and Lebourdy,¹⁴ nor a combination of accelerator depression and vagus stimulation, as suggested by Rothlin.² Our reasons for this belief in the case of animals have been stated elsewhere,¹⁰ and we believe that they receive additional support from our experiments on human subjects. With man, as with dogs, small doses of atropine completely prevented or abolished the slowing due to ergotamine. After atropinization there was no evidence of a paralysis or depression, partial or complete, of the accelerator nerves, and the pulse rate was increased to as great a degree as with atropine alone. Hamet⁴⁰ made a similar observation. Slight stimuli were sufficient to cause a distinct increase in the pulse rate after the injection of ergotamine. The action of ergotamine on the sympathetic system is known to be slow, and in our experiments a considerable time elapsed before the effect of the drug was observed, yet in animals the action was almost immediate after intravenous injection. A prompt action has been observed by those who have injected the drug intravenously in man. In our experiments the action of the drug seemed stronger in the subjects with evidence of a strong vagus tone (sinus arrhythmia). The appearance of this arrhythmia after the administration of ergotamine, when not present before the injection, is also suggestive of a vagus action. Certain of the subjective symptoms, such as nausea and vomiting, are in favor of a vagal effect. Finally, in view of the large amounts of ergotamine that are known to be necessary to affect the accelerator nerves in animals, the doses that can be used clinically would scarcely seem sufficient to produce the decided slowing of the heart observed in man, by a depression of the accelerator nerves. The belief that ergotamine slows the heart by an action of the vagus has also been expressed by Wetterwald.²²

The increase in blood pressure in the normal subjects was of about the same magnitude as the changes in the pulse rate and was probably due to the same mechanism by which ergotamine causes a rise in blood pressure in animals. A primary blood pressure raising (vasoconstrictor)

40 Hamet, R. Les principes actifs de l'ergot et leur action pharmacologique, *Presse med* 35 1605, 1927

effect was observed by Dale and Spiro⁴¹ and ascribed by them to a stimulation of the arterial musculature. According to Rothlin,² this effect, which may be the sole result of small as well as the initial effect of large doses, is due to a stimulation of the sympathetic ganglions. However, the effect of ergotamine on the blood pressure in animals is most variable. In addition to inhibiting and reversing the effects of epinephrine, in which marked individual and species variations occur, and the primary blood pressure raising effects described by Dale and Spiro⁴¹ and Rothlin,² Salant, Nadler and Brodman⁴² have observed a primary blood pressure lowering effect. This was apparently due to an associated action of the natural epinephrine in the body, since it failed to appear when the suprarenals were removed. According to Dale and Spiro,⁴¹ the primary blood pressure raising effect of ergotamine may fail to appear if the arteries are in a state of increased tonus at the moment of injection. This may serve to explain the failure of some authors to obtain an effect when dealing with subjects (patients) in whom the pressure was already elevated. It is also possible that the observations of Salant, Hadler and Brodman may explain the fall in blood pressure obtained in some subjects, particularly those with an elevated pressure. Nevertheless, it is probable that the lowering of the blood pressure obtained by most authors with human subjects was due to a lengthening rest period and failure to secure basal readings at the start of the experiment.

The results of our experiments raise the question whether, in man, ergotamine possesses the same action on the sympathetic nervous system as has been described in animals. There can be no doubt that in animals ergotamine in sufficient dosage exerts a depressant action on many of the motor functions of the sympathetic nervous system and probably on some of the inhibitory functions as well. As we have stated many times, however, such effects are obtained in animals with doses and experimental conditions that are not permissible in the case of human subjects. The failure of ergotamine to affect certain of these functions in man may be attributed in part to the necessary use of small doses, which are ineffective. On the other hand, certain of the results observed may be attributed to the different action of small, as compared with large doses.

However, another and more significant explanation is suggested for the failure of ergotamine to affect certain functions of the sympathetic system in normal subjects under basal conditions. The work of Cannon

41 Dale, H. H., and Spiro, K. Die Wirksamen alkaloides des Mutterkorns, *Arch f exper Path u Pharmacol* **95** 337, 1922.

42 Salant, W., Nadler, J. E., and Brodman, K. Circulatory Reactions to Ergotamine and Effect upon Them Produced by Adrenalectomy and the Blood pH, *Proc Soc Exper Biol & Med* **25** 361, 1927-1928.

and his associates⁴³ seems to show that in animals, under conditions of quiet and repose (i.e., basal conditions), certain functions of the sympathetic system are inoperative. Cannon's view, which is somewhat opposed to the theory of a constant activity of the sympathetic system balanced against the parasympathetic system, postulates a condition of homeostasis which may be modified on need by the sympathetic system, which is called into play when the need arises. "One may consider total inactivity of the exteroceptive system as a basal state for the organism, i.e., a condition for minimal functioning of both the exteroceptive and enterofective systems. Whenever the exteroceptive system becomes active an internal disturbance is produced or tends to be produced, and associated therewith the basal enterofective function is increased in order to maintain homeostasis. It should be clear from the foregoing considerations that if the organism is maintained in a fairly constant basal condition, i.e., if there is not marked disturbance of the internal environment because of response to external stimuli, there is relatively little need for the functioning of the enterofective system." On the basis of such an hypothesis it is not surprising that ergotamine, granting it is a depressant of the sympathetic system, should fail to exhibit any effect on certain functions of the latter under basal conditions. The functions of a mechanism that is inoperative can scarcely be depressed or paralyzed. The best evidence in favor of this explanation for the ineffectiveness of ergotamine is its effect on the blood sugar. The failure of ergotamine to affect the accelerator nerves of the heart, which, in contrast to other parts of the sympathetic system, may be assumed to be in a state of constant activity, need not of necessity conflict with this explanation in view of the well known resistance of these nerves to small doses of ergotamine. In fact, this resistance of the accelerator nerves may be related to the degree of their tonicity. Analysis of the experimental evidence in respect to the action of ergotamine suggests that it is the weaker sympathetic functions that are the more readily affected by the drug. Such a possibility may explain why ergotamine, although it fails to lower the production of heat of normal subjects, because of the relative inactivity of the sympathetic system under basal conditions,⁴⁴ fails also in some instances when the production of heat is increased above the basal level by the action of the

43 Cannon, W. B. Organization for Physiological Homeostasis, *Physiol Rev* 9:399, 1929, The Sympathetic Division of the Autonomic System in Relation to Homeostasis, *Arch Neurol & Psychiat* 22:282 (Aug) 1929.

44 Cannon, W. B., Newton, H. F., Bright, E. M., Menkin, V., and Moore, R. M. Some Aspects of the Physiology of Animals Surviving Complete Exclusion of Sympathetic Nerve Impulses, *Am J Physiol* 89:84, 1929.

sympathetic system. It is conceivable that under the latter conditions the tonic activity of the sympathetic system may be so great as to make it relatively insusceptible to the amounts of the drug that can be used. Thus may be explained the conflicting results on the basal metabolism which have been obtained clinically in some disease states.

In the case of the rise in blood pressure seen in normal subjects under basal conditions, the absence of activity of the sympathetic system is of no significance, since the effect is apparently due to the vasoconstrictor or stimulant action of small doses of ergotamine, as previously stated. The reported lowering of the blood pressure in some abnormal subjects may be the result of the action of the drug on a sympathetic function which is active. Failure to secure a reduction in some patients with an elevated pressure, as in some of our patients with thyrotoxicosis, may be due to a relatively too great tonus of the sympathetic system.

The explanation that we have suggested would serve not only to account for the behavior of ergotamine as observed in our experiments, but also to explain many of the apparently conflicting results which appear in the literature on ergotamine. The results of some additional but uncompleted studies seem to offer further evidence in its support. Should this explanation prove to be correct, our results offer some evidence that in man the function of the sympathetic system is similar to that described by Cannon in animals.

The reaction to the drug, especially the muscular soreness and fatigue, is of some interest. While no adequate explanation for these symptoms is to be found in our experiments, it is suggested that the muscular soreness may be the result of the action of the drug on the smaller arteries and the arterioles of the muscles, causing a relative and temporary ischemia. Such a possibility is of interest in view of the gangrene which is a characteristic feature of the toxic action of ergot (and ergotamine). Neither gangrene nor any other serious untoward effect was observed in any of the normal subjects or patients, although some of the latter were given ergotamine over considerable periods of time. Toxic symptoms, including gangrene, have, however, been reported in patients who were treated with ergotamine⁴⁵.

SUMMARY AND CONCLUSIONS

Ergotamine, in single doses of 0.5 mg subcutaneously, was without significant effect on the basal metabolic rate or fasting blood sugar level of normal human subjects. The pulse rate was slowed, and the blood

45 Schonbauer, L. Zur Behandlung des Morbus Basedow mit Ergotamin (Gynergen), *Deutsche Ztschr f Chir* 198:99, 1926.

pressure, the diastolic pressure in particular, was slightly but definitely elevated

The administration of 1 mg of ergotamine by mouth, three times daily, over a period of several days, also failed to influence to a significant degree the basal metabolic rate of these subjects

Similar effects were noted in patients with thyrotoxicosis, although the effect on the pulse rate and blood pressure was generally greater. A somewhat greater individual variation in the response of the pulse rate and blood pressure to ergotamine was noted among the patients than among the normal subjects

It is suggested that the failure of ergotamine to influence certain functions of the sympathetic system is due to the fact that in normal subjects under basal conditions these parts of the sympathetic system are inoperative and are therefore insusceptible to the action of ergotamine. This explanation, if correct, may serve to explain certain conflicting reports appearing in the literature. However, many of the reported instances of lowered heat production, pulse rate and blood pressure following the administration of ergotamine should not be attributed to the action of the drug, but to failure to secure a truly basal condition at the beginning of the experiment

Under the conditions of our experiments, the slowing of the pulse cannot be attributed to a depression or paralysis of the accelerator nerves of the heart, but is the result of a stimulating or sensitizing action on the vagus

PELLAGRA SECONDARY TO BENIGN AND CARCINOMATOUS LESIONS AND DYSFUNCTION OF THE GASTRO-INTESTINAL TRACT

REPORT OF THIRTEEN CASES¹

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Pellagra as a complication of a lesion or of dysfunction of the digestive tract is assuming greater significance in view of the increasing number of cases reported. Rolph¹ first called attention to the possibility of pellagra originating under these circumstances in 1916, when he reported a case of carcinoma of the upper third of the stomach, involving the cardiac orifice and associated with pellagra. Other instances of benign and malignant lesions with secondary pellagra have been reported by Bryan,² Bender,³ Nuzum,⁴ Joyce and Seabrook,⁵ Barnes,⁶ Elliott,⁷ Klauder and Winkelman,⁸ Cabot⁹ and one of us

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¹ From the Division of Medicine and Section on Dermatology and Syphilology, the Mayo Clinic

1 Rolph, F W Cancer of the Stomach and Pellagra in the Same Patient, *Canad M A J* **6** 323 (April) 1916

2 Bryan, R C Cancer of the Stomach with Associated Pellagra, *Virginia M Monthly* **46** 107 (Aug) 1919

3 Bender, W L Pellagra Secondary to Lesions of the Stomach Interfering with Nutrition, *J A M A* **84** 1250 (April 25) 1925

4 Nuzum, F R Pellagra Associated with Annular Carcinoma of the Terminal Portion of the Ileum, *J A M A* **85** 1861 (Dec 12) 1925

5 Joyce, T M, and Seabrook, D B Stricture of the Rectum as an Indirect Cause of Pellagra, *Northwest Med* **24** 284 (June) 1925

6 Barnes, J M Typical Pellagra Syndrome Developing in a Patient with Chronic Ulcerative Colitis While Under Hospital Treatment, *Ann Clin Med* **4** 552 (Jan) 1926

7 Elliott, A R Pellagra Secondary to Carcinoma of the Colon, *M Clin North America* **11** 237 (July) 1927

8 Klauder, J V, and Winkelman, N W Pellagra Among Chronic Alcoholic Addicts, *J A M A* **90** 364 (Feb 4) 1928

9 Cabot, R C A Case with Anasarca, Cyanosis, Symmetrical Dermatitis Diarrhea, Mass in the Abdomen and Psychosis, *Boston M & S J* **197** 1319 (Jan 12) 1928

(P A O'L)¹⁰ One of the most recent contributions from the pellagrous belt is that of Turner,¹¹ in which he reported sixteen cases of the disease associated with diverse lesions of the gastro-intestinal tract, eight of which were strictures of the rectum. One of the purposes of this report is to bring up to date the reports of cases that have come under our observation.

The diagnostic and therapeutic significance of the secondary forms of pellagra and the serious prognostic significance of the complication in the event an operation is contemplated are of immediate concern to the internist. Undoubtedly a number of cases of secondary pellagra have been encountered that have not been reported, others probably have been overlooked, including cases in which there are constitutional symptoms but no cutaneous manifestations of the disease, that is, pellagra sine pellagra.

The fact that the disease may develop as the result of obstructive gastro-intestinal lesions, of voluntary restriction of food for various reasons or of chronic alcoholic addiction, as emphasized by Klauder and Winkelman, Sweitzer¹² and Shattuck,¹³ is the explanation for its distribution without geographic limit and its appearance as a complicating factor often when least expected. This is in contrast to the primary idiopathic form of the disease, which is limited to the southern states, Central America, Mexico and to such outlying possessions of the United States as the Canal Zone.

In the classic case, there are characteristic lesions of the skin, mouth and tongue, provoking sore tongue and often dysphagia, gastro-intestinal disturbances in the form of abdominal pain or discomfort, diarrhea, proctitis, often nausea and vomiting and symptoms referable to the central nervous system. The convenient diagnostic triad of dermatitis, diarrhea and dementia is more alliterative than scientific, for the dementia may appear only in the advanced stages of the disease.

Those who are familiar with the disease advise considering the possibility of pellagra in cases of chronic gastric disturbance with venal exacerbations, when obscure abdominal symptoms referable to the appendix, ovaries or gallbladder are present, in cases of dysentery, neurasthenia, melancholia, eczema, sunburn or chapping of the arms, face, neck or feet and in cases of persistent dizziness, epileptiform seizures and vaginitis. The dermatologists recommend that when one

10 O'Leary, P. A. Secondary Types of Pellagra, *M. Clin. North America* **10** 647 (Nov.) 1926.

11 Turner, R. H. Pellagra Associated with Organic Disease of the Gastro-Intestinal Tract, *Am. J. Trop. Med.* **9** 129 (March) 1929.

12 Sweitzer, S. E. Pellagra and Alcoholism, *Minnesota Med.* **11** 719 (Nov.) 1928.

13 Shattuck, G. E. Scurvy, Pellagra and Sprue at the Boston City Hospital, *New England J. Med.* **199** 986 (Nov. 15) 1928.

is confronted with a patient complaining of obscure constitutional symptoms, one should not be satisfied until all cutaneous lesions, when any are present, have been carefully differentiated. Unsystematic or hurried examinations, failure to elicit a history of "sunburn" in suspicious cases and unfamiliarity with the appearance of the residual cutaneous lesions may make it difficult for the internist to interpret the associated phenomena. As a matter of fact, the dermatologist's recognition of the pellagious nature of the lesions or residues in their various types and stages on several occasions has led to the disclosure of gastrointestinal lesions in patients not residing in the pellagious zone or the discovery of lesions which previously had escaped the notice of the examining physician. Moreover, as illustrated in three of Turner's cases, the clinician may overlook gross organic disease in the upper part of the digestive tract in the presence of a well established case of pellagra. Such an error would seem more excusable in localities where the disease is endemic.

In a previous report, one of us (P. A. O'L.)¹⁴ showed that in the type of pellagra encountered at this clinic the dermatitis has not been so extensive or so severe as that usually observed in pellagious districts. The well defined limitation, particularly about the wrists and the forearms, suggesting the term "gauntlet" or "glove" dermatitis, is highly characteristic of the disease, as are the well defined borders of hyperkeratosis and the residual pigmentation on the face and neck. In the acute phase the eruption may vary from blotchy erythema to extensive bullous lesions, with associated edema, whereas, in the latent and receding stages, a dry, scaling and, at times, keratotic eruption may be seen. Residual pigmentation at the periphery of the lesion is a characteristic feature of the less acute forms. Casal's "necklace," dermatitis of the anterior part of the neck, is often of diagnostic aid. Secondary infection, fissuring and ulceration may be unpleasant complications.

The recognition of pellagra is not difficult if the general symptoms that arise from involvement of the skin, the gastro-intestinal tract and the nervous system are borne in mind. From the dermatologic point of view, chronic eczematoid dermatitis, allergic dermatitis, erythema solare, erythema multiforme, lupus erythematosus of the disseminate type and ringworm must be excluded in the differential diagnosis. The problem is not difficult if the other characteristics of pellagra are demonstrable. The dermatitis, with the exception of the form pellagra sine pellagra, is essential to the diagnosis.

In spite of extensive research and great familiarity with the clinical aspects of the disease, including exhaustive pathologic studies, an extensive review of the literature still reveals a lack of unanimity con-

14 O'Leary, P. A. Pellagra. A Study of Thirty-Four Cases in Localities Where Pellagra Is Not Endemic, *Northwest Med* 27:319 (July) 1928.

cerning the etiology of the disease. Some of those who are familiar with the acute, active endemic forms of the disease remain unconvinced that it is purely a dietetic deficiency disease. We also have observed a small group of patients in whom the disease developed while apparently they were partaking of a well balanced diet, amply adequate in calories and vitamins. Experimental, pathologic and clinical evidence undoubtedly supports the contention of Goldberger and his co-workers¹⁵ and of other authorities, that pellagra has its origin in a deficient dietary. Recently, Findlay¹⁶ confirmed Goldberger's researches and concluded that when rats are fed food lacking the thermostable vitamin G (the pellagra preventive, P-P, factor of Goldberger) a condition resembling black tongue in dogs and pellagra in man results. Denton,¹⁷ in a convincing pathologic study of twelve fatal endemic cases of pellagra in the Canal Zone, reemphasized the fact that the pathologic characteristics of the lesions of pellagra give no insight into the origin and cause of the disease. His experience showed that the disease is one in which the lesions are confined to the epithelial surfaces, without extension to the deeper tissues or organs. These lesions give no evidence of being infectious, the changes in the alimentary canal do not appear to be simple inflammatory changes, and some underlying and contributory factor must be necessary for their production. Singer and Pollock¹⁸ and others stated that the changes in the central nervous system are likewise essentially retrograde and degenerative, and not inflammatory, in both the acute and the chronic stages. Denton also maintained that the lesions of the mouth, tongue and esophagus are the most constant and consistent lesions of the disease and, although perfectly analogous to the cutaneous lesions, are not so ephemeral. He expressed the belief that this fact argues against the photodynamic hypothesis of Jobling and Arnold,¹⁹ which maintains that a fungus, *Aspergillus glaucus* or *Aspergillus repens*, was the indirect cause of the photosensitiveness responsible for the dermatitis, and that a deficient diet permitted an overgrowth of the organism. In Bass'²⁰ experience, exposure not only to sunlight but to heat, pressure, trauma and irritating chemicals is

15 Goldberger, Joseph, Wheeler, G. A., Lillie, R. D., and Rogers, L. M. A Further Study of Experimental Blacktongue with Special Reference to the Blacktongue Preventive in Yeast, Pub. Health Rep. **43** 657 (March 23) 1928.

16 Findlay, G. M. Pellagra-Like Lesions Associated with Deficiency of Vitamin B₂ in the Rat, J. Path. & Bact. **31** 353, 1928.

17 Denton, James. The Pathology of Pellagra, Am. J. Trop. Med. **5** 173 (March) 1925.

18 Singer, H. D., and Pollock, L. J. The Histopathology of the Nervous System in Pellagra, Arch. Int. Med. **11** 565 (June) 1913.

19 Jobling, J. W., and Arnold, Lloyd. Observations and Reflections on the Etiology of Pellagra, J. A. M. A. **80** 365 (Feb. 10) 1923.

20 Bass, C. C. Pellagra, M. Clin. North America **12** 1181 (March) 1929.

capable of producing the cutaneous lesions, especially when the cause is active at the proper stage and period of activity of the general disease. The clinical evidence supporting the theory of dietetic deficiency, especially in the secondary forms of pellagra, seems convincing and is manifest in various ways. The pellagra of patients with mental disease may be the result of an unbalanced or inadequate institutional diet or the actual refusal of food over long periods of time due to the capricious appetites of psychotic persons. It is also likely that in some cases that develop in hospitals for the mentally defective, the cutaneous lesions are slow to develop. The voluntary restriction of food as a measure of reducing weight, dietary restriction in the treatment for acne, in functional gastric disorders, in "elimination" diets to determine the food allergen, in the treatment for "intestinal toxemia," following abdominal operation in the elderly patient and for no tangible or adequate reason, as in the case reported by Carley,²¹ give rise to the disease.

The development of pellagra in the presence of gastro-intestinal lesions, malignant or benign, as in the cases herewith reported, and especially in the obstructive type, is an established fact. The obstructive lesion would appear to play especially a mechanical rôle in that it prevents the ingestion or retention of sufficient food or of food containing adequate vitamins. In gastro-intestinal lesions without obstruction, as in gumma of the stomach and ulcerative colitis, the development of pellagra, even when the patient is taking highly nutritious food, as Barnes observed, may be due to actual deficiency in protein as the result of inadequate absorption and assimilation in the presence of such lesions. The continued use of alcohol over a period of several weeks or months favors the development of the secondary form of the disease through gastro-intestinal upsets, anorexia and eventual semistarvation. The important part played by dietetic imbalance or inadequacy is evidenced by the improvement, often prompt, in the less severe forms of pellagra effected by the timely institution of a proper dietetic regimen or by the surgical removal of the obstruction, if the patient survives operation. The restricted diets are composed mostly of carbohydrate, and the histories often show that patients have subsisted almost entirely, over a considerable period of time, on such combinations as "milk toast, bread and cake," "toast and crackers," "milk, ice cream and bread," "oatmeal porridge and potato soup," and other combinations of a similar nature. Several patients had not eaten fresh meat for periods as long as ten years, and they were complete strangers to fresh vegetables and fruits. The effectiveness of a proper diet, even in advanced, hopeless cases, so far as the primary lesion is concerned, is exemplified in Elliott's case, in which carcinoma of the colon recurred nine years after

²¹ Carley, P. S. A Case of Pellagra Following Voluntary Restriction of Diet, *J. A. M. A.* 91: 879 (Sept 22) 1928.

the original operation, and in which the pellagrous lesions were severe. These disappeared five weeks after dietetic treatment was begun, and there was no recurrence of the lesions, in spite of the fact that the patient died as the result of extensive metastasis nine months after his last admission to the hospital.

Turner cited the investigations of Rolly and Liebermeister,²² more recently confirmed by Arnold and Brody,²³ which apparently furnish, from an experimental standpoint, certain phenomena observed in pellagrous persons. It is somewhat difficult to explain the infrequency of pellagra in the vast number of patients with obstructing, malignant and inflammatory lesions of the digestive tract who have been forced to subsist on a restricted diet in order to be comfortable. Crutchfield²⁴ stated that pellagra is rarely seen in patients who are not suffering from some previous contributory disease that disturbs metabolism, and Shattuck expressed the belief that although in recent years much light has been thrown on the causes of pellagra and that a great deal can now be done toward prevention and cure, much more must be learned about the gastro-intestinal secretions and the factors that influence assimilation of food in this disease. Apparently other conditions, independent of the actual gastro-intestinal lesions, in which the assimilation of food is disturbed may give rise to secondary pellagra, this is exemplified in an unusual case of nutritional disturbance with osteomalacia and tetany, reported by Constam and Partch.²⁵ Such observations suggest the possible causative rôle of the inadequate gastric digestion of protein as demonstrated by Castle²⁶ in pernicious anemia, with its characteristic achylia gastrica, and possibly in many cases of sprue. However, the depression or complete cessation of gastric secretory function could be a secondary phenomenon and not essential in pellagra as it is in pernicious anemia.

Of a total of fifty-four cases of pellagra, the majority of which were of a mild, chronic form and in which the diagnosis was confirmed by dermatologists, fractional analysis of gastric content after a test meal

22 Rolly and Liebermeister, G. Experimentelle Untersuchungen über die Ursachen der Abtötung von Bakterien im Dunndarm, *Deutsches Arch f klin Med* **83** 413 (Sept.) 1905.

23 Arnold, Lloyd, and Brody, Louis. Bacterial Flora and Hydrogen Ion Concentration of the Duodenum, *J Infect Dis* **38** 249, 1926.

24 Crutchfield, E. D. Pellagra. With Special Reference to the Skin and Mucous Membrane, *Arch Dermat & Syph* **17** 650 (May) 1928.

25 Constam, G. R., and Partch, W. T. An Unusual Case of Nutritional Disturbance Showing Symptoms of Pellagra, Osteomalacia and Tetany, *Minnesota Med* **12** 40 (Jan.) 1929.

26 Castle, W. B. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. Effect of Administration to Patients with Pernicious Anemia of Contents of the Normal Human Stomach Recovered after Ingestion of Beef Muscle, *Am J M Sc* **178** 748 (Dec.) 1929.

disclosed the absence of free hydrochloric acid in 79 per cent. In 62 per cent of Guthrie's²⁷ unselected cases of pellagra, gastric hydrochloric acid was absent. In our entire group there were a few cases of achlorhydria in which it was difficult to distinguish between pellagra and pernicious anemia until the effect of an antipellagious diet on the lesions and hemopoietic function was determined. On the basis of our experience and that of many others, it is justifiable to state that when achlorhydria is persistently present, especially when it is associated with secondary anemia, asthenia, nervous irritability and diarrhea, the possibility of pellagra should be borne in mind, whether or not a history or evidence of cutaneous lesions is obtainable. Spue should also be considered. At the same time, it is essential to determine whether or not dietetic shortcomings are in any way responsible for the condition.

Again, reverting to the endemic forms of pellagra, one is reminded of Wilkerson's²⁸ belief that malnutrition is the curse of the South. To this he attributes the early physical decay of many rural southerners of both sexes. His observations as to the kind of food and the preparation of food in many homes, not excluding those of the well-to-do, should make physicians and health authorities circumspect and not take for granted the patient's statement that his diet is adequate. Wilkerson called attention to the monotony of the diet, the excess of fat often used in the preparation of meats and vegetables, especially the former, and the excessive cooking of the latter. Whether or not this has any bearing on the matter, it is interesting to note that our latest case of pellagra occurred in a young girl who lived in a nonpellagrous region, but in whom a severe case developed while she was taking a ketogenic (low carbohydrate and high fat) diet for treatment for epilepsy.

TREATMENT

It is essential to determine, if possible, and to correct the exciting factor in secondary types of pellagra. The majority of such cases are the result of malignant and benign obstructing lesions of the upper part of the digestive tract as well as of unsuccessful or unwarranted operative procedures provoking marked motor or secretory dysfunction or both. Cases of obstruction usually require surgical intervention unless the condition is obviously inoperable. However, the risk is greatly enhanced, especially in cases in which malignant growths are present or in cases with high grade obstruction of whatever nature, because adequate pre-operative preparation to combat malnutrition, dehydration and alkalemia, so essential to recovery, is extremely difficult in the presence of compli-

²⁷ Guthrie, J. B. Pellagra, Hydrochloric Acid in the Stomach Contents, *Am J Trop Med* **6** 357 (Sept.) 1926.

²⁸ Wilkerson, F. W. Dietetic Difficulties in the South, *M Clin North America* **12** 1479 (March) 1929.

cating pellagra. An earnest but careful attempt to readjust the diet should precede any attempt to remove the lesion or the cause of the dysfunction. In the early or favorable cases it is often possible to eliminate the pellagrous manifestations by intensive dietetic measures. In our experience it is necessary, after a successful operation, to prepare for the toxemia or dementia of pellagra as soon as it is feasible, even in the milder cases, as this complication invariably occurs within from three to seven days after operation. Several cases proved fatal without marked evidence of toxemia or psychosis. In some of the cases reported, removal of the obstruction alone was largely responsible for the improvement of the pellagrous features. Apparently a great deal depends on the extent to which digestive function can again be restored within reasonable limits. Outstanding results have been accomplished in the cases in which it has been possible to establish and maintain a diet high in vitamins by means of rare lean meat, yeast, the juices of citrus fruits, strawberries, apples, grapefruit, liver, salmon, eggs, milk and cream, cod liver oil and such green vegetables as spinach, lettuce, asparagus, fresh peas, cabbage and tomatoes. As the requisites of a normal diet must also be met, enough calories to maintain the body weight and sufficient bulk to obviate constipation should be furnished. The use of wheat bread and cereals may make up for the deficiency of carbohydrate in other foods. If necessary, in the presence of an ulcerative gastric lesion the vegetables and fruits which should be served may be cooked and pureed. At times it is feasible to administer food frequently and in small amounts. Owing to the digestive disturbances present and the aversion to food which some patients have, it is essential that the physician be persistent, and, if necessary, that he urge or coerce the patient to take an adequate amount. Iron and arsenic have been recommended and used by some authorities, although they are not of much proved value. Application of bland lotions in the acute phase of the dermatitis is of value and is stimulating. Mild keratolytics may be used during the periods of latency and chronicity. Complications are treated as they arise. It might be added that the vitamin content of the food should be gradually increased, reaching the maximum in about a week, and that the patient should be kept ambulatory as much as possible, although prolonged exposure to sunlight should be avoided. It is essential to impress the patient with the possibility of recurrence and to urge that he partake of a diet rich in proteins and vitamins for several years.

Details concerning the thirteen cases are contained in the accompanying table, and in the reports of the cases. In two of the cases the diagnosis was questionable, one of the patients was an elderly man, with pyloric obstruction, the result of benign gastric ulcer, and cholecystic disease, the other patient was a woman, aged 45, with a rather

diffuse syphilitic lesion of the stomach. The evidence was suggestive enough to influence us to include them in the series. With two exceptions, all of the patients lived in the north temperate zone. The cutaneous lesions were not as marked in any case as those that occur in active acute endemic cases. Apparently, however, the extent of the dermatitis is not a criterion as to prognosis for the mortality was

Pellagra Secondary to Lesions of the Gastro-Intestinal Tract

Case	Lesion or Cause of Disturbance on	Age	Sex	Duration, Months	Pellagra, Distribution of Lesions	Stomach and Glands	Diarrhea	Nervous symptoms	Psychosis	Presence of Hydrochloric Acid	Operation	Result
1	Pyloric obstruction (duodenal ulcer)	64	M	6	Hands, wrist, face and neck	—	—	0	—	—	—	Died
2	Pyloric obstruction (carcinoma)	63	M	2	Hands, wrists and face	—	—	—	—	0	—	Died
3	Pyloric obstruction (duodenal ulcer, carcinoma)	44	M	1½	Hands and wrists	—	—	—	—	0	0	Not traced
4	Duodenal ulcer and malfunctioning gastro-enterostomy	35	F	5	Hands, wrists and face	—	—	—	0	0	—	Died
5	Duodenal ulcer and malfunctioning double gastro-enterostomy	44	M	1	Hands, wrists, forehead and nose	—	—	—	—	0	—	Cured
6	Pyloric obstruction (multiple gastric ulcers, chronic cholecystitis)	62	M	1	Hands and wrists	—	—	—	0	0	—	Died
7	Large gastric ulcer, jejunal feeding	46	F	½	Hands	—	—	—	0	—	—	Cured
8	Gastric syphilis	45	F	2	Hands and wrists	—	—	—	—	0	0	Cured
9	Esophageal stricture, pyloric ulcer	28	F	2½	Hands, wrists and face	—	—	—	—	—	0	Died
10	Unnecessary gastro-enterostomy	45	M	5	Hands, wrists and face	—	—	—	0	0	0	Cured
11	Unnecessary gastro-enterostomy	46	M	4	Hands and wrists	—	0	—	—	0	—	Cured
12	Carcinoma of descending colon	55	M	1	Hands, wrists, face and neck	—	—	0	—	—	0	Died
13	Therapeutic colitis	21	F	1	Hands and wrists	—	—	—	—	—	0	Improved

high, especially in the surgical group, in spite of the fact that every precaution was taken. It is to be noted that in ten of the thirteen cases reported the lesions were benign. Of the five patients who were submitted to laparotomy, five had benign lesions of which four were complicated and there was an unfavorable termination in all but two.

REPORT OF CASES

CASE 1.—A man, aged 64, had had gastric disturbances for a number of years at intervals of from two to six months. The symptoms were suggestive, although not characteristic, of chronic peptic ulcer with recent obstructive features

Prior to admission to the clinic he had been under treatment for ulcer for five weeks and had obtained considerable relief. Thirty-two years previous to admission, he had had pulmonary tuberculosis, and thirty years before admission he had undergone an operation for tuberculous fistula in ano. This was followed by a stormy convalescence, and one month later spontaneous rupture occurred, and then, purulent material was passed, apparently from the rectosigmoid. In the summer of 1928, diarrhea was present at frequent, brief intervals. For six months prior to admission, the patient's diet was markedly reduced. He lost 20 pounds (9 Kg). There was dark discoloration and dryness of the hands and forearms, associated with marked general weakness, moderate depression and apathy.

Examination revealed evidence of malnutrition, marked dehydration, severe oral sepsis, definite physical signs of an old tuberculous process in the upper lobe of the right lung, moderate tenderness and rigidity in the right upper quadrant of the abdomen, normal reflexes and sensations and anal scars. The skin of the gauntlet areas of both hands and wrists was sharply delineated, pigmented and slightly keratotic, but without erythema. Laboratory investigations disclosed gastric hyperacidity. There was roentgenologic evidence of deformity of the duodenal bulb, with considerable residue of barium after six hours. A few polyps of the sigmoid were seen through the proctoscope.

After preliminary preparation, posterior gastrojejunostomy was performed for a subacute, perforated duodenal ulcer and marked pyloric obstruction. A poor prognosis was given on account of the complicating pellagra. On the eighth day after operation, ileus, gastric retention and marked prostration developed. In spite of energetic measures the patient died four days later, death was preceded by dementia and coma.

Necropsy revealed a healthy operative field, the evidence of old, healed tuberculosis of the upper lobe of the right lung, pulmonary embolism with infarction of the lower lobe of the right lung and pleuritis. Also, there were mucopurulent enteritis and healed, ulcerative sigmoiditis and proctitis.

Comment—In this case, with reliable evidence of pellagra, at least from a dermatologic standpoint, there was associated gastric hyperacidity. The dermatitis had retrogressed considerably within a week after the operation. It is probable that our endeavor to supply a diet high in meat protein and vitamins precipitated the gastric retention. At no time prior to death was there evidence of a sudden onset of acute dyspnea and cyanosis characteristic of pulmonary embolism. Although there was no history of sore mouth, and although the diarrhea had preceded the dermatitis by a considerable period and did not persist, the disclosures at necropsy would support rather than cause rejection of the diagnosis of pellagra. Denton maintained that the colon is the site of pathologic changes in all cases of pellagra and that diarrhea seems to follow chiefly on changes in the sigmoid and rectum. In this case, it is probable that the changes found may have had a tuberculous origin in view of the history of the case. The grave risk of operation on patients with pellagra and the futility and harmfulness even of an early and adequate regimen pushed too zealously perhaps, are well exemplified in this case.

CASE 2—A man, aged 63, gave a history of progressively severe gastric disturbances of one year's duration, associated with loss of weight, appetite, strength and color, and aggravation of constipation of long standing. He had been on a milk diet exclusively for six months. Only rarely since the onset of his illness had he attempted to eat solid food, and invariably he had only chewed and expectorated it because it was distasteful. Two months prior to admission, "sunburn" developed on the backs of both hands and lesions appeared on the cheeks and nose. A local physician had prescribed ointment for the former.

On examination the patient was found to be emaciated and dehydrated, and 43 pounds (19.5 Kg.) under his usual weight. He was anemic. The concentration of hemoglobin was 55 per cent, and the erythrocytes numbered 3,740,000 per cubic millimeter of blood. A firm, somewhat flattened, slightly mobile, nonsensitive mass was palpated in the upper part of the epigastrium. Laboratory investigations revealed achlorhydria and gastric retention, a filling defect in the pars pylorica characteristic of medullary carcinoma and a large residue of barium after six hours. The cutaneous lesions, symmetric and sharply demarcated, were considered typically pellagrous.

After five days' preparation, partial gastrectomy was performed. A carcinoma measuring 10 by 8 by 2 cm. was removed, including the involved regional lymph nodes. For four days, the postoperative convalescence was uneventful and the cutaneous lesions improved noticeably. Then diarrhea appeared and persisted, accompanied by dementia, on and after the fifth day. In spite of energetic measures, circulatory collapse developed, the patient became maniacal and died on the seventh day following the operation. Necropsy disclosed the operative field to be healthy. Acute enteritis and degenerative changes were present in the posterior columns of the spinal cord.

CASE 3—A man, aged 44, had had periodic attacks of indigestion simulating duodenal ulcer for more than seven years. For three months prior to admission to the clinic, the symptoms had become more marked. The usual measures for relief from pain and discomfort, by giving food and alkalis, were progressively less effectual, and there were periods of nausea and vomiting of unduly retained food, progressive loss of weight and strength and habitual constipation. Six weeks prior to admission, the patient experienced severe diarrhea, which lasted two weeks. Also, there were stomatitis and lesions involving the dorsum of the hands and wrists, presenting the characteristic gloved appearance. Nervous irritability, depression, insomnia, uncertain gait attributed to marked weakness, emaciation and anemia were also present.

Examination of the gastric contents revealed the absence of free hydrochloric acid in all of the specimens removed by the fractional method, and evidence of motor impairment of low grade. Roentgenoscopic examination gave evidence of a small filling defect on the lesser curvature and pars media, characteristic of carcinoma. A semisolid diet, totaling 2,200 calories daily, including 5 Gm. of Harris' brewers' yeast, caused marked improvement, especially in the diarrhea and the cutaneous manifestations. Operation was deferred, and at the time of the patient's departure the cutaneous lesions had entirely disappeared.

The patient was admitted later to a hospital in another state because of increasing gastric discomfort and retention, undoubtedly the result of a malignant lesion of recent origin in the pyloric antrum.

Comment—The chief features in this case were evidence of pyloric obstruction due to a malignant lesion, first regarded as benign, a history of dietetic inadequacy, pellagra characterized by diarrhea and

lesions of the mouth, hands and wrists, nervous and mental disturbances, cachexia, and anemia

CASE 4—A woman, aged 58, who had borne twelve children, first consulted us in 1913, because of pelvic and digestive disturbances of several years' duration. The digestive symptoms were suggestive of duodenal ulcer.

Examination revealed deformity of the duodenal cap. Gastro-enterostomy had been done elsewhere in 1922. For nine months prior to the patient's second admission to the clinic, in March, 1926, she had a recurrence of her original ulcer-like symptoms, in addition to painful epigastric seizures, with wide radiation and associated chills, nausea, vomiting, residual soreness and loss of weight and strength. She was emaciated and anemic (hemoglobin 58 per cent and erythrocytes 3,590,000), there were tenderness, protective spasm throughout the epigastrium and right upper quadrant of the abdomen and possibly a mass in the latter region. The evidence suggested a poorly functioning gastro-enterostomy stoma requiring surgical intervention.

At operation, the stoma was found to be small, almost completely obstructed and situated within about 3 cm. of the pylorus. There was a mass in the pylorus, regarded as the result of an old inflammatory process. The old gastrojejunal anastomosis was disconnected and a new one was made in the usual situation. As the jejunum was small and considerably traumatized, the surgeon, at the completion of the operation, believed that extensive resection would have given better ultimate results.

The postoperative course was characterized by the onset of stomatitis and lesions on the dorsums of both hands and wrists. Three months later characteristic dermatitis of glove-like distribution was found. The patient had been living on cereals and bread only, for about a year. These lesions disappeared on treatment, but the stomatitis and tendency to vomit persisted. A third examination, two months later, revealed a serious condition, with evidence of marked involvement of the nervous system, depression, gastric motor disturbances and alkalemia. In spite of energetic treatment the patient failed rapidly, and death was preceded by ileus, persistent vomiting, cyanosis and collapse. Permission for necropsy was refused.

CASE 5—A man, aged 44, entered the clinic in October, 1924. He gave a history of having had gastric disturbances intermittently for fifteen years. Gastro-enterostomy, performed elsewhere nine months prior to admission in the clinic, had given relief for a month. A second operation, performed by another surgeon seven months prior to admission, caused subsidence of the gastric pain, but vomiting, of the kind seen in retention, and diarrhea ensued. Simultaneous with the onset of the diarrhea, a month prior to admission, the patient noted dermatitis on the backs of the hands and forearms, glossitis and marked loss of weight.

Examination revealed pellagrous lesions on both hands and wrists, the forehead and the nose. There was achlorhydria and roentgenologic evidence of two gastro-enterostomy openings, as well as deformity of the duodenal cap. *Trichomonas hominis* and *Endameba histolytica* were present in the feces. A culture of the feces for *Aspergillus* gave negative results.

Operation disclosed extensive perigastric adhesions involving the upper part of the intestinal tract. There were two gastro-enterostomy openings, with a sharp kink of the intestine between them. Both anastomoses were disconnected, and pylorotomy was performed because of the presence of a hard, indurated, duodenal ulcer. Temporary jejunostomy was made just below the lower opening in the

jejunum, which had been closed, and this permitted feeding by tube. The jejunostomy wound closed spontaneously when the tube was removed three weeks after operation. Delirium and dementia developed on the third day after operation and lasted a fortnight. Institution of a proper diet, including fruit juices, brewers' yeast and puréed green vegetables, was followed by rapid recovery from the mental disturbances and gradual disappearance of the cutaneous lesions and diarrhea. The patient returned for examination a year later and was found to be in perfect health.

CASE 6—A man, aged 62, entered the clinic on June 14, 1926. He gave a history of having had gastric disturbances for five years, characterized by epigastric discomfort, pyrosis, intolerance for acidulous fruits and constipation. For a year he had had a sense of impaired gastric motility with regurgitation of food which had necessitated the restriction of his diet to soups and liquids for six months prior to admission. He had lost weight.

Examination disclosed moderate emaciation, secondary anemia, achlorhydria and evidence of gastric retention. Considerable fresh and altered blood was found in the gastric content. There was roentgenologic evidence of an obstructing lesion at the pylorus. Bilateral, symmetric lesions were noted on the dorsums of the hands, these lesions had been present for a month and were highly suggestive of pellagra.

At operation, two small ulcers were excised from the lesser curvature and pars media of the stomach. These were found to be benign on microscopic examination, although carcinoma was suspected because of anacidity and retention. The gallbladder was distended, and there was evidence of marked pericholecystitis. The gallbladder was removed because it was causing compression and twisting of the first portion of the duodenum and was probably the causative factor in the gastric retention.

Convalescence was uneventful. After a period of improvement, the patient again suffered a relapse, complaining of asthenia, epigastric soreness, anemia, inability to gain weight, migrating arthralgia and poor circulation. Five months later, analysis of the gastric content revealed anacidity, but there was no evidence of a lesion on roentgenologic examination. Death occurred ten months after operation. Necropsy was not obtained. The patient's wife reported that the deceased "just continued to dry up and finally starved to death." The presence of cutaneous lesions was not mentioned.

CASE 7—A married woman, aged 46, came under our observation on June 17, 1929. She gave a history of two attacks of illness, following dietary indiscretions, in February and May, 1929, when she passed tarry stools, associated with considerable prostration. On the last occasion transfusion of 1 liter of blood had been necessary. Anemia had been present since the last hemorrhage.

Examination revealed moderate secondary anemia, the presence of free hydrochloric acid in the gastric content and roentgenologic evidence of an ulcerating lesion high in the cardiac end of the stomach, which, because of its size, was thought to be malignant.

On June 22, operation disclosed a freely movable ulcerated lesion in the fundus of the stomach, surrounded by an inflammatory mass about 7 cm. in diameter. Jejunostomy after the method of Witzel was made, and jejunal feedings were instituted.

Diarrhea appeared a month prior to the patient's second admission, in September. This was followed, two weeks later, by acute proctitis, acute stomatitis and glossitis and roughening and fissuring of the knuckles of both hands. The cuta-

neous lesions were sharply delineated. The pellagrous nature of the lesions was verified, and they were attributed to inadequate jejunal feedings, owing to a misrepresentation of instructions on the part of the patient. The concentration of hemoglobin was 67 per cent, and the erythrocytes numbered 4,710,000. The concentration of hydrochloric acid in the gastric content was somewhat reduced. The patient was given a diet high in vitamin G, including scraped beef, fresh fruit juices, dried brewers' yeast and salmon. The daily intake of food was equivalent to 2,400 calories. The patient's weight was maintained on this regimen. There was marked and rapid improvement in the lesions of the skin and mucous membranes. The size of the gastric lesion remained unchanged.

In November, a third examination revealed an increase in weight of 16 pounds (7.3 Kg). The anemia persisted, and, owing to the local discomfort caused by the jejunal tube, it was removed. Meals with a high content of vitamin and iron were resumed without incident. The lesion in the stomach was reduced in size, the stomach was more flexible in the region of the lesion and the patient was in much better spirits. In February, 1930, examination showed that the patient had regained her normal weight, the anemia had disappeared, the acidity of the gastric content was normal, there were no subjective complaints and the roentgenologic examination revealed persistence of a niche, reduced somewhat further in size.

Comment—In this case, there was a deficiency disease, with cutaneous lesions of a pellagrous nature, as the result of postoperative jejunal feedings in the presence of a large lesion situated high in the stomach. The lesion may have been benign or malignant, it was not feasible to remove it at the time of operation.

CASE 8—A woman, aged 45, entered the clinic in October, 1927, complaining of gastric disturbances of about ten years' duration. Her diet had been markedly restricted for a long time, and at times she had been unable to retain even water. The condition had been diagnosed previously as hour-glass stomach on the basis of an apparent syphilitic gumma. Antisyphilitic treatment was instituted, but in spite of improvement, the patient eliminated vegetables, fruit and meat from her diet to a large extent.

Examination revealed an anemic, markedly undernourished woman. There were achlorhydria and a filling defect rather characteristic of syphilis in the pyloric antrum, and the Wassermann reaction of the blood was strongly positive. There was evidence of "fading" pellagrous dermatitis on the dorsa of both hands. Marked symptomatic improvement, barring a temporary setback caused by exfoliative dermatitis of low grade, followed antisyphilitic treatment and a suitable diet.

Comment—In our opinion a patient with advanced gastric syphilis is an excellent candidate for grave nutritional disturbances and especially for pellagra. Frequently there is marked contracture of the stomach with corresponding reduction in its capacity, anacidity, anorexia, inability as the result of coincident involvement of the liver and cachexia. It is to partake of food in adequate amounts, grave metabolic disturbances possible that evidences of pellagra frequently have been overlooked in such persons.

CASE 9—A married woman, aged 33, entered the clinic on March 8, 1922. There was a background of a psychoneurotic family history. The patient was

nervous and asthenic, and her married life was unhappy. She gave a history of severe hematemesis and melena eight years prior to admission. This had been attributed to gastric ulcer by a local physician. For six years prior to admission she had given evidence of mental derangement, apparently of the manic-depressive type. Five months prior to coming to the clinic she attempted to commit suicide by drinking strong lye. This was followed by marked progressive obstruction of the esophagus, which necessitated liquid nourishment given in small amounts. Owing to her depression she often refused nourishment in any form, and this resulted in marked loss of weight and strength. Three previous, unsuccessful attempts at dilatation of the esophagus had been made. Three weeks prior to admission, there had been an onset of diarrhea, stomatitis, glossitis and symmetric dermatitis on the backs of both hands, extending to the wrists, with sharp demarcation.

On examination the patient was found to be apathetic, prostrated and emaciated. Introduction of a bougie revealed a rather dense stricture of the esophagus, the first obstruction was 30 cm. below the incisors and the second, 5 cm. lower. These strictures were gradually dilated so that food could be swallowed freely. The diarrhea persisted, bronchopneumonia developed two weeks after admission, and death occurred five days later. Necropsy revealed chronic inflammation of the esophagus, with constricting scars and multiple diverticular formations, chronic pyloric gastritis with an old healed ulcer, advanced emaciation with terminal bronchopneumonia and pellagrous lesions on the skin of the hands and wrists.

Comment—It is our opinion that this is the only instance in the available literature of pellagra secondary to benign stricture of the esophagus.

CASE 10—A man, aged 45, was admitted to the clinic in November, 1923. He had had gastric disturbances over a period of twenty years which were suggestive of duodenal ulcer, and for which the gallbladder and appendix had been removed elsewhere in 1919, without relief from symptoms. Six months later, gastro-enterostomy had been performed by the same surgeon. The original symptoms still persisted, and the constipation, which had been present before the operation, was replaced by from eight to fifteen loose bowel movements a day. There was also considerable loss of weight and strength, followed by depression and nervousness. Five months prior to admission, the following lesions appeared: symmetric dermatitis, glove-like in distribution, with marked pigmentation, a circumoral eruption having a brownish-black, maculopapular, pigmented appearance, marked erythema of the gums and edges of the tongue and bilateral circumscribed areas of suprapatellar infiltration. Dermatologic examination confirmed the belief that the lesions were pellagrous. The patient had refrained from the use of milk, cream and fruits for years, and owing to loss of appetite and to discomfort after meals since the last operation, he had eaten little.

Laboratory investigations revealed achlorhydria. Roentgenologic studies of the stomach, duodenum and colon gave no evidence of gross disease, barring slight deformity and contraction of the region of the anastomosis in the stomach. On a diet high in vitamins and the intramuscular administration of sodium cacodylate, the cutaneous lesions disappeared within a month, and the diarrhea was markedly lessened. The epigastric discomfort persisted in variable degree.

The patient was examined again about four years later, chiefly because of depression with the obsession of threatened mental disorders and the fear of doing violence to his family. A neuropsychiatric survey did not result in a

diagnosis of actual psychosis, and there was no tangible evidence of recurring pellagra. Amebas in both vegetative and encysted forms, resembling *Endameba histolytica*, and other protozoa were found in the stool, acetarsone was prescribed. Administration of dilute hydrochloric acid in orangeade and institution of a diet with low residue caused prompt and marked improvement.

CASE 11—A man, aged 48, was admitted to the clinic in August, 1924. He gave a history of gastric disturbances, suggestive of a chronic gastric ulcer, that had been present for twenty-three years. Gastro-enterostomy had been performed, and the appendix had been removed in 1914. This was followed for a year by daily vomiting of food and of a profuse quantity of greenish, sour fluid. His condition gradually improved, but gaseous distress and constipation persisted. There was no marked dietetic imbalance, although he "watched his diet carefully to avoid stomach trouble." In the spring of 1923, and also in 1924, symmetric, erythematous areas appeared on the dorsa of both hands extending to the wrists, the condition was not relieved by wearing gloves. These lesions at first were maculopapular, but they shortly became vesicular. Residual, brownish pigmentation and lichenification were noted at the borders of the patches. Three months prior to admission, paresthesia of the upper and lower extremities appeared and persisted. In addition, weakness and depression, later associated with vertigo and syncope for a short period, and disturbances of speech and respiration were noted.

Examination revealed some malnutrition, moderate anemia, septic tonsils, prolapsed, tender and bleeding hemorrhoids and achlorhydria. There was no roentgenologic evidence of gastric ulcer or duodenal deformity, and the stomach appeared to be functioning normally. Ligation and excision of the internal hemorrhoids two months after admission were followed by satisfactory convalescence. In the following spring, the patient's local physician treated him for a third vernal attack of "pellagrous dermatitis" without associated diarrhea, stomatitis or mental disturbances. To successive business reverses were also attributed the recurrence of gastric disturbances and asthma. The dermatitis responded promptly to a diet high in vitamins, in which fresh meat, fresh fruits, yeast and fresh vegetables figured prominently.

CASE 12—A man, aged 55, had been losing weight and strength for eighteen months prior to admission. For six months he had been unable to work, and during that time he had lost the difference between 218 (97.7 Kg) and 135 pounds (61.2 Kg). For three months prior to admission he had complained of distress, usually in the region of the left hypochondrium, which came immediately after eating. Finally, the pain became more and more constant, but it was still aggravated by the taking of food. As a result, the patient had, for four or five weeks, limited his diet to oatmeal, a little milk and soup made of beans and potatoes. During this time there was persistent diarrhea. Shortly before he came to the clinic he noticed a cutaneous eruption.

Examination showed the patient to be emaciated and depressed. The tongue was reddened and glazed. There were some pulmonary emphysema, many large hemorrhoids and some edema of the legs. Typical acute lesions of pellagra involved both wrists, the face and the neck. A neurologic examination disclosed nothing abnormal. Roentgenologic examination gave evidence of a small filling defect in the descending colon. The urine contained some albumin and hyaline casts. The concentration of hemoglobin was 57 per cent, and the erythrocytes numbered 4,200,000. In spite of efforts made to give him more food, he failed rapidly and died ten days after admission. At necropsy the pathologist found

a carcinoma of the descending colon. The lesion had perforated into the pelvis of the left kidney. Fatty changes in the liver and evidence of old healed tuberculous pleuritis and lymphadenitis in the thorax were found.

CASE 13—A woman, aged 21, was admitted to the clinic in September, 1927. There was definite clinical evidence of severe ulcerative colitis of ten months' duration, with marked anemia, complicated by erythema nodosum and acute polyarthritis in both knee joints. Hospitalization for these complications had been necessary at home prior to coming under our observation. After three months' treatment, the patient had improved somewhat and was dismissed. Owing to her failure to cooperate properly, she found it necessary to return to the clinic in January, 1928, with evidence of peripheral neuritis, apparent dementia, marked emaciation and weakness. In spite of energetic treatment in the hospital, the following signs developed: fever and marked contracture of both legs, progressive emaciation, severe stomatitis and marked psychosis and purposeless tremors involving the muscles of the face and arms. The condition of the bowels was satisfactory. Eight months after the original admission, lesions on the hands and wrists, characteristic of pellagra, were first noticed. These may have been present before in milder degree. On institution of proper dietetic measures, with adequate amounts of food containing vitamin G, mental improvement and a gain in weight were recorded. A month after the patient's return home her nurse reported marked general improvement.

Comment—Barnes reported a case of fatal pellagra, developing in a patient with chronic ulcerative colitis, in which the pellagious lesions were of a much more severe degree than those seen in this case. They involved the feet and face, in addition to the hands and wrists, and occurred while the patient was under dietetic treatment for colitis in the hospital.

SUMMARY

Pellagra developed in eight patients with obstructing benign lesions or dysfunction (late, after operation) of the upper part of the digestive tract, in two with obstructing carcinomatous lesions, in one with gastric syphilis and in two with lesions of the colon (one carcinomatous, one inflammatory). This secondary form of pellagra tends to support the theory that dietetic deficiency is the cause of the disease. In the cases reported, the clinical manifestations of the disease were not as marked as those of the active, endemic type of pellagra. Treatment may be ineffectual in cases with mechanical obstruction or in those with marked impairment of motility of the upper part of the digestive tract, until the mechanical condition is corrected. Surgical intervention is attended by high mortality. Case reports covering the essential clinical features are submitted.

II THE GALACTOSE TOLERANCE TEST IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE *

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In a previous article¹ dealing with the metabolism of galactose, we discussed the work of various investigators and detailed some of our own observations leading to the conclusion that galactose offers the best means of investigating the carbohydrate function of the liver. We do not consider it adequate as a routine test for liver function, on the contrary, its limitations are definite, and it is precisely these limitations that enable it to serve a special purpose, that of an aid in the differential diagnosis of jaundice.

The discovery of the glycogenic function of the liver in 1857 by Claude Bernard at once stimulated the interest of clinicians as well as physiologists and pathologists in the question of carbohydrate metabolism. This interest was soon manifest in an extensive literature, and the idea of utilizing the sugars for testing hepatic function was a natural outgrowth. Such attempts, however, resulted in divergent results, and, particularly during the last quarter of the nineteenth century, created a controversy between the German and French schools. The German school, notably Quincke,² von Noorden,³ Kraus and Ludwig,⁴ and Bloch,⁵ was unable to demonstrate any marked or constant reduction of tolerance for sugar in hepatic disease, the French school, on the other

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1 Shay, H, Schloss, E M, and Bell, M. The Metabolism of Galactose. Considerations Underlying the Use of Galactose in Liver Function Tests, Arch Int Med, to be published

2 Quincke, H. Symptomatische Glycosurie, Berl klin Wchnschr **13** 529 and 547, 1876

3 von Noorden, F. Pathologie des Stoffwechsels, Berlin, August Hirschwald, 1893, p 274

4 Kraus, F, and Ludwig, H. Klinische Beiträge zur alimentaren Glycosurie. Wien klin Wchnschr **4** 855, 1891

5 Bloch, G. Ueber alimentare Glycosurie. Ztschr f klin Med **22** 525, 1893

hand, including Achard and Castaigne,⁶ Baylac,⁷ and Bierens de Haan,⁸ favored the sugars as test substances for hepatic function. Strauss⁹ attempted to explain and partially reconcile these divergences on the basis of the various sugars and amounts of sugars used as test substances.

The extent and character of liver activity in carbohydrate metabolism may be briefly summarized as follows:

- 1 The conversion of monosaccharides (dextrose, levulose, galactose) brought to the liver cells by the blood, into glycogen, a polysaccharide closely related to starch
- 2 The temporary storage of glycogen, as such
- 3 The reconversion of glycogen into dextrose by liver enzymes, as need arises for sugar throughout the body
- 4 The vital character of this function

It is with this last mentioned character, only recently definitely established, that we are most concerned. As early as 1874, Bock and Hoffman¹⁰ indicated the importance of the carbohydrate function of the liver. These investigators found a diminution of blood sugar after the liver had been removed or shunted from the circulation. Many observers have repeated these experiments, but it remained for the classic investigations of Mann and his co-workers¹¹ to establish the importance of this function of the liver. They found that immediately after the removal of the liver, the blood sugar decreases progressively, when it reaches a certain rather definite limit, of from 0.06 to 0.04 per cent, a characteristic group of symptoms appears, and, if allowed to continue, death soon ensues. Mann showed that these phenomena could be controlled by the injection of dextrose, and that the duration of the control, within certain limits, depended on the amount of dextrose administered. Mann¹² definitely stated that the removal of the liver completely severs a part of the vital normal process of carbohydrate metabolism.

6 Achard, C, and Castaigne, J. L'épreuve de la glycosurie alimentaire et ses causes d'erreur, *Arch. gén. de méd.* **1** 27, 1898.

7 Baylac, J. De la valeur de la glycosurie alimentaire dans le diagnostic de l'insuffisance hépatique, *Compt. rend. Soc. de biol.* **4** 1065, 1897.

8 Bierens de Haan, J. C. J. Ueber alimentare Glykosurie bei Leberkranken, *Arch. f. Verdauungskr.* **4** 4, 1898.

9 Strauss, H. Zur Funktionsprüfung der Leber, *Deutsche med. Wchnschr.* **27** 757, 1901.

10 Bock, C, and Hoffman, F. A. Experimental Studien über Diabetes, Berlin, H. E. Olven, 1874.

11 Mann, F. C, and Magath, T. B. Studies on the Physiology of the Liver. II. The Effect of the Removal of the Liver on the Blood Sugar Level, *Arch. Int. Med.* **30** 73 (July) 1922.

12 Mann, F. C. Modified Physiologic Processes Following Total Removal of the Liver, *J. A. M. A.* **85** 1472 (Nov. 7) 1925.

It is readily seen from a brief review of the literature that investigations of the use of the sugars in testing liver function were productive of widely variant results and equally divergent interpretations. However, the fact seems to have been completely overlooked that nature, in providing for so vital a faculty, has characteristically created an organ with adequate reserve, such a reserve as may be demonstrated in the kidney, the lung, etc. Then, too, little consideration was given the remarkable power of regeneration of the liver cells, as a result of which, in chronic damage of these cells, one may see cellular regeneration and degeneration proceeding simultaneously. It is because of these two properties, adequate reserve and a strong tendency to regeneration, that in cases of slow or local disease of liver cells there is sufficient actively functioning liver tissue to maintain the carbohydrate mechanism. From these considerations, it becomes obvious that one should expect changes in the carbohydrate function of the liver only when all or nearly all the liver cells are damaged more or less acutely or when chronic damage of these cells has progressed extensively and regeneration has failed. This contention is strengthened by the experiments of Roubitschek,¹³ who found marked galactosuria in animals poisoned with phosphorus, not only was the acute diffuse damage of the liver cells, reflected in this galactosuria, but in those cases in which, despite additional poisoning with phosphorus, there was a recession of the galactosuria, postmortem examination revealed regeneration of the liver cells. These facts, then, of adequate hepatic reserve and ready hepatic regeneration aid in the clarification of the variable results that have attended the efforts to utilize the carbohydrate function as a routine test of liver function. The very limitations of this type of test, however, form the basis for its use in the differential diagnosis of jaundice.

As we have previously indicated, a derangement of the carbohydrate function of the liver might be expected in acute or subacute diffuse damage of the liver cells, this type of disease is usually accompanied by jaundice. Such a derangement of function might, then, be used in identifying those cases of jaundice due to acute or subacute diffuse damage of the liver cells, in other words, the toxic and infectious types of jaundice. It is this group that has clinically presented the greatest difficulty of early recognition. In these cases, none of our laboratory procedures offer much aid in diagnosis. It was hoped, at one time, that the qualitative van den Bergh reaction would serve to identify and differentiate the various types of jaundice, this very group of toxic and infectious

13 Roubitschek, R. Alimentare Galaktosurie bei experimenteller Phosphorvergiftung, *Deutsches Arch f klin Med* 108 225, 1912

cases proved to be its Waterloo. The need for a means of identifying this type is apparent. We shall attempt to demonstrate in this report of our preliminary series that the carbohydrate function test serves to identify this group and to differentiate it from the obstructive and hemolytic types of jaundice. For this purpose, the galactose tolerance test has been used. It was chosen on the basis of the superiority of galactose over levulose in testing liver function. The interpretation has been based on the urinary output of galactose since, for the present at least, this appears to serve as the best measure of the utilization of galactose by the liver.¹

TECHNIC OF GALACTOSE TOLERANCE TEST

This test was introduced by Richard Bauer, of Vienna, in 1906.¹⁴ The following is the method as we have employed it at the Jewish Hospital in Philadelphia for the past two years.

The test is preceded by a twelve hour fast, and the patient receives no breakfast. On the morning of the test, the patient voids, this specimen is examined qualitatively for sugar. Pure galactose, exactly 40 Gm, dissolved in about 500 cc of water, usually flavored with a few drops of lemon juice, is administered orally. The patient voids completely at the next successive five hours, and the specimens are collected in toto and labeled. Since Cori¹⁵ has shown that the rate of absorption of the sugar is independent of both the absolute amount and the concentration of the sugar in the intestine, the patient may have as much water as desired during the test, but nothing else. If specimens are not obtainable on the hour, they are secured as close as possible to the hour periods. The important point is that all urine voided during the five hour period following the ingestion of the galactose is to be collected.

Determination of Galactose Excreted—1 In Nondiabetic Persons. Each of the specimens obtained at the hourly period is tested qualitatively for sugar. The positive specimens are then mixed, the total quantity measured, and a quantitative determination of sugar is carried out by the Benedict method. The total amount of galactose excreted in the urine is then calculated.

A word may not be amiss here as to whether the sugar excreted in the urine after the ingestion of galactose is actually galactose. The resistance of the sugar excreted to fermentation by yeast, its convertibility to mucic acid (Bauer,¹⁶ MacLean and de Wesselow¹⁷) and its greater rotating effect on polarized light have been factors in its identification.

14 Bauer, R. Ueber die Assimilation von Galaktose und Milchzucker beim Gesunden und Kranken, Wien med Wchnschr **56** 20, 1906.

15 Cori, C. F. The Fate of Sugar in the Animal Body. The Rate of Absorption of Hexoses and Pentoses from the Intestinal Tract, J Biol Chem **66** 691, 1925.

16 Bauer, R. Weitere Untersuchungen ueber alimentare Galaktosurie, Wien med Wchnschr **56** 2538, 1906.

17 MacLean, H., and de Wesselow, O. L. V. The Estimation of Sugar Tolerance, Quart J Med **14** 103, 1921.

In one study, its actual isolation from the urine (Halberkann and Kahler¹⁸), with a comparison of the sugar obtained with pure galactose, including the melting point, formation of osazone and the conversion of mucic acid, has established the identity of the excreted sugar as galactose

2 In Diabetic Persons It is obvious that the question of the utilizability of this test in diabetic persons should arise Bauer,¹⁶ in one of his earlier papers, doubts its efficiency in such cases Our¹ studies, however, indicate that the utilization of galactose by the liver is independent of the condition of the pancreas By applying the method suggested by Somogyi¹⁹ for the separation of galactose from dextrose in the blood, we have been able to do so satisfactorily in the urine This method is dependent on the rapid fermentation, by a yeast suspension, of dextrose, as compared to that of galactose Care must be exercised in the preparation of the yeast suspension, as commercial yeast is always contaminated with adhering particles of wort which contain nonfermentable reducing substances A weighed amount of fresh commercial yeast is suspended in from five to ten parts of water, this is centrifugated, and the water decanted This operation is repeated until the supernatant liquid is practically clear and colorless, and fails to show the presence of any reducing substances when tested with Fehling's solution The yeast is then ready for use, and a 10 per cent suspension is prepared

In dealing with this test in a diabetic person, the quantitative determination of sugar is carried out in the usual manner as described, and the total amount of sugar is estimated The urine and yeast suspension are then mixed in the proportion suggested by Somogyi for the blood, namely, 1 part of urine and 7 parts of the 10 per cent yeast suspension (To correct as nearly as possible for the actual volume of yeast in the suspension, an allowance of 10 per cent of the suspension is made, e g, if 1 cc of urine is used, 7.7 cc of the 10 per cent suspension of yeast is added, allowing the 0.7 cc for the volume of yeast cells in the suspension) We have experimented with smaller proportions of yeast, but have not obtained satisfactory fermentation The mixture is then incubated for forty-five minutes By this method, we have been able to obtain a complete destruction of the dextrose in solution, while the loss of galactose has not exceeded 10 per cent Therefore, for all practical purposes, the determination of the sugar remaining after such fermentation, represents the galactose excreted during the tolerance test The difference between this determination and the reading before fermentation represents the amount of dextrose present These results of fermentation are practically identical with those obtained by Corley,²⁰ using the Shaffer-Hartmann micromethod for determination

CLINICAL APPLICATION OF THE GALACTOSE TOLERANCE TEST

In a previous contribution,¹ we presented evidence that the normal tolerance for galactose ranges between 37 and 40 Gm The normal person, then, in whom there is no disturbance of the carbohydrate function

18 Halberkann, J, and Kahler, H Beitrage zur Leberfunktionsprufung Isolierung und Identifizierung der mit dem Harn angeschiedenen d-Galaktose, Ztschr f phys Chem **154** 34, 1926

19 Somogyi, M Reducing Non-Sugars and True Sugar in Human Blood, J Biol Chem **75** 33, 1927

20 Corley, R C Factors in the Metabolism of Lactose The Disposal of Intravenously Administered Galactose in the Rabbit, J Biol Chem **74** 1, 1927

of the liver, may excrete from 0.0 to 3.0 Gm of galactose in the five hour period following the ingestion of 40.0 Gm of that sugar. In cases of jaundice due to factors other than acute diffuse damage of the liver cells, sufficient active liver tissue is present to carry on carbohydrate metabolism. Thus, obstructive or hemolytic jaundice gives readings within the normal range. On the other hand, in jaundice accompanying acute diffuse damage of the liver cells, the carbohydrate function is impaired, and the liver, unable to utilize the normal quantity of galactose, allows a quantity of this sugar, larger than normal, to pass and reach the general circulation. In the absence of a kidney threshold for galactose,¹ this excess appears in the urine. Hence, in jaundice with sufficient damage of liver cells, quantities of galactose greater than 3 Gm appear in the urine in the five hours following the ingestion of 40.0 Gm of this sugar.

A review of the literature on the reported cases studied with the galactose tolerance test reveals many points of interest. While it is, we believe, beyond the province of this paper to discuss these cases in detail, certain observations of such a review warrant discussion. Bauer in his earlier work¹⁶ thought that he had found a test for cirrhosis of the liver. It was not until two years after his first publication that he²¹ reported the finding of an alimentary galactosuria in catarrhal jaundice. He reported at this time a series of ten cases of catarrhal jaundice in which the alimentary galactosuria became evident early in the illness, increased somewhat during its course, and decreased as the jaundice disappeared. We have noted practically identical observations in the present series of cases.

Considerable confusion arises in reviewing the literature, because of the different values for the normal standards that various authors have adopted for the test. Neugebauer²² and Maliwa²³ considered as pathologic an output of over 0.6 Gm after the ingestion of 40.0 Gm of galactose. Reiss and Jehn²⁴ and Wagner²⁵ permitted an output of 2.0 Gm under the same conditions to be accepted as normal. Most investiga-

21 Bauer, R. Ueber alimentare Galaktosurie bei Ikterus, *Deutsche med Wchnschr* **34** 1505, 1908.

22 Neugebauer, H. Zur Pathogenese des Icterus catarrhalis, *Wien klin Wchnschr* **25** 514, 1912.

23 Maliwa, E. Bemerkungen zur Galaktose Intoleranz, *Med Klin* **18** 762, 1922.

24 Reiss, E., and Jehn, W. Alimentare Galaktosurie bei Leberkrankheiten, *Arch f klin Med* **108** 187, 1912.

25 Wagner, F. Klinische Untersuchungen ueber die Bedeutung der verschiedenen Zuckerproben fur die Beurteilung der Leberfunktion, *Ztschr f klin Med* **80**.174, 1914.

tors, including ourselves, have followed Bauer, who considered outputs of 3.0 Gm and more as indicative of impaired hepatic tolerance.

Worner,²⁶ up to 1919, had collected from various authors 165 cases of catarrhal jaundice in which the galactose tolerance test had been performed. Of these, 133, or 80.5 per cent had shown a urinary output greater than 3.0 Gm during the test. In 132 collected cases of icterus due to tumors and gallstones, 9, or 6.8 per cent gave readings above 3 Gm. We quote the preceding figures, largely to point out that we do not believe that they represent a fair estimate of the test, in spite of the favorable appearance of the percentages. The element of chance works against the test in both groups of cases. Mild cases of catarrhal jaundice are not infrequently encountered, it has been our experience with this type that the carbohydrate function of the liver is comparatively slightly altered and tends to recover rapidly. In such cases, if the test happens to be delayed a few days, an apparently normal result may be obtained. Cases of chronic damage of the liver cells (tumor, cirrhosis, etc.), it must be remembered, can also reach the state in which the carbohydrate function of the liver may show impairment. The report of Reiss and Jehn²⁴ illustrated such an instance clearly. They cited a case of cirrhosis of the liver in which they obtained an output of 3.9 Gm during the test. Studying the clinical notes accompanying this case, we find recorded a mild icterus of the skin and sclera, and intermittent fever. Only a few days after the galactose reading of 3.9 Gm was obtained, autopsy showed a liver that grossly was entirely devoid of normal structure and microscopically presented a severe cirrhosis with areas of necrosis of the liver tissue. The point that we desire to make becomes obvious—that under any condition in which the liver reserve for carbohydrate function is destroyed there will be an abnormal galactose tolerance. It also becomes apparent that in such a group of cases as is represented by the above mentioned instance, no functional tests are necessary to help make the diagnosis. Another point worthy of mention at this time is that we must not overlook the fact that a so-called “catarrhal jaundice” may complicate the courses of many cases of chronic damage of the liver cells. We experienced such an instance in a case of cirrhosis in which a high galactose output was given during the jaundice but which returned to normal limits as the jaundice subsided.

All of the various conditions in which a high galactose output is reported fall in the group in which diffuse damage to the liver cells of an

²⁶ Worner, H. Die praktische Bedeutung der Galaktoseprobe, *Med Klin* 15 1142, 1919.

TABLE 1—Results of Galactose Tolerance Tests in Toxic and Hemolytic Jaundice

Patient	Age	Diagnosis	Basis for Diagnosis	Type of Jaundice	Duration of Jaundice	Qualitative Reaction	Quantitative	Dose in Mg per Kg per Cent	Retention, per Cent	Galactose Tolerance Test, Gm
1	8	Catarrhal jaundice	Clinical	Toxic	7 days	Biphasic	6.9	5	30	4.56
2	11	Catarrhal jaundice	Clinical	Toxic	7 days	Delayed direct	14.4	5	100	5.37
3	18	Catarrhal jaundice	Clinical	Toxic	11 days	Delayed direct	13.4	5	40	10.75
4	18	Catarrhal jaundice	Clinical	Toxic	27 days	Delayed direct	9.3	5	100	3.50
5	9	Catarrhal jaundice	Clinical	Toxic	13 days	Delayed direct	1.3	2	0	3.30
6	53	Catarrhal jaundice	Clinical	Toxic	15 days	Delayed indirect	12.8	2	100	5.50
7	53	Catarrhal jaundice	Clinical	Toxic	37 days	Biphasic	0.7	2	60	3.80
8	9	Catarrhal jaundice	Clinical	Toxic	12 days	Negative	1.9	5	0	5.18
9	31	Lung abscess with toxic hepatitis	Clinical	Toxic	2 days	Negative	4.5			1.60
10	9	Catarrhal jaundice	Clinical	Toxic	2 days	Biphasic	9.6			11.30
11	9	Catarrhal jaundice	Clinical	Toxic	Jaundice gone					9.00
12	10	Catarrhal jaundice	Clinical	Toxic	?	Negative	1.6	5	5	3.60
13	12	Catarrhal jaundice	Clinical	Toxic	2 days	Delayed indirect	10.6			5.05
14	6	Catarrhal jaundice	Clinical	Toxic	7 days	Delayed indirect	1.0			6.91
15	6	Catarrhal jaundice	Clinical	Toxic	3 days					3.65
16	6	Catarrhal jaundice	Clinical	Toxic	?	Delayed direct	5.2			3.02
17	19	Catarrhal jaundice	Operation	Toxic	9 weeks	Biphasic	16.3			3.48
								Average		5.11
1	26	Chronic hemolytic jaundice	Clinical	Hemolytic	Several years	Negative	1.6			0.00
2	5	von Jaksch's anemia	Clinical	Hemolytic	?	Negative	3.2			0.50
3	6	Chronic hemolytic jaundice	Clinical	Hemolytic	6 years	Negative	3.5			0.50
4	6;	Perniciou anemia	Clinical	Hemolytic	?	Negative	1.6			0.50
								Average		0.13

acute nature has doubtlessly occurred. Catarrhal jaundice is most frequently reported, while asphenamine jaundice, acute yellow atrophy, phosphorus poisoning, syphilitic hepatitis and jaundice associated with lead poisoning as well as with various acute infections make up the list of other types of cases in which this test has been found positive.

The appended tables of our series of cases are divided into hemolytic toxic and obstructive jaundice. The column "duration of jaundice" indicates the duration of the jaundice at the time at which the galactose tolerance was obtained. The last column indicates the number of grams of galactose excreted during the five-hour test period. A glance at the average output of each of the groups of jaundice presented will justify much that has been stated in the foregoing paragraphs.

CONCLUSION

We believe that the galactose tolerance test offers a means of identifying early the group of toxic or infectious jaundice, a group of cases that often tax the diagnostic acumen of the keenest clinicians. In the preliminary presentation of the aforementioned group of thirty-nine cases of various types of jaundice, we feel that the results are sufficiently striking to warrant further and more general investigation.

SUMMARY

The observations in thirty-nine cases of jaundice have been presented. On the basis of the galactose tolerance test performed in each case, the presence or absence of acute or subacute diffuse damage of the liver cells has been determined, and wherever possible, confirmation of diagnosis has been made by operation, biopsy or autopsy. The basis for the use of a sugar tolerance test in differentiating these groups of cases of jaundice has been described, the differentiation is attributed to the diffuse destruction or derangement of the hepatic cells, with consequent disruption of the carbohydrate mechanism on the one hand and the survival of sufficient functioning tissue to maintain so vital a process on the other. The reasons for the choice of galactose as the test sugar have been discussed in a previous paper²⁷. The technique of the galactose tolerance test as used in these investigations is given

27 Shay, H., Schloss, E. M., and Bell, M. A. Metabolism of Galactose. I. Considerations Underlying the Use of Galactose in Tests of the Function of the Liver, *Arch. Int. Med.* **47**: 391 (March) 1931.

IV THE DIFFUSIBLE CALCIUM OF THE BLOOD STREAM IN TETANY *

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AND

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The reduction of calcium in the blood in infantile tetany and in tetany due to parathyroid deficiency has been well recognized since the classic work of McCallum and Voegtlin¹. On the other hand, no significant alteration in the total amount of calcium in the serum has been found in tetany induced by hyperventilation or by an overdosage of bicarbonate². The differences in the analytic observations of the chemical composition of the blood in tetany of diverse origin³ led Grant and Goldman to conclude "Tetany occurs under so many circumstances that it probably cannot be attributed to a single etiological factor". This, however, has not deterred many from attempting to establish a common disturbing factor as the cause of all forms of tetany. Two hypotheses have been proposed with respect to the etiologic factors responsible for tetany. 1 All forms of tetany are due to an alkaline shift in the acid-base balance. 2 A lowering of the calcium ion concentration is

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1 McCallum, W G, and Voegtlin, C. On the Relation of the Parathyroid Gland to the Calcium Metabolism and to Tetany, *J Exper Med* **11** 118, 1909

2 Grant, S B, and Goldman, A. Tetany Following Forced Respiration in Man, *Am J Physiol* **52** 209 (June) 1920

3 Grant (footnote 2) McCallum, W G, and others. Effect of Pyloric Obstruction in Relation to Gastric Tetany, *Bull Johns Hopkins Hosp* **31** 1 (Jan) 1920. Harrop, G A. Production of Tetany by Intravenous Infusion of Sodium Bicarbonate, *ibid* **30** 62 (March) 1919

the cause of tetany in all cases. The results of experiments carried out by us and others do not bear out either of these hypotheses as the sole factor responsible for tetany, and we must concur with Giant and Goldman that tetany cannot be attributed to any single etiologic factor.

The experiments carried out by us support the view that infantile and parathyroprival tetany are associated with a lowering of the physiologically available calcium of the blood stream. In our experiments this is demonstrated by a decrease in the diffusible fraction of the serum calcium. In contradistinction, tetany due to hyperventilation and an overdosage of a bicarbonate are induced by an alkaline shift in the acid-base balance of the blood without an accompanying decrease in the physiologically available calcium. In fact, our experiments showed high levels for the diffusible calcium in this form of tetany.

INFANTILE AND PARATHYROID TETANY

In previous communications we pointed out that the accumulated data show that the calcium in the blood stream is present practically only in the plasma, and that there it exists in several forms that are measurable by analytic methods. These fractions are the diffusible calcium, or the fraction able to pass through a membrane impermeable to colloids, and the nondiffusible calcium, the fraction held back by a membrane impermeable to colloids. The diffusible fraction contains the ionic blood calcium and the nondiffusible calcium is in all probability combined with the plasma proteins in a nonionized compound. The amount of nondiffusible calcium, then, may vary with the changes in the plasma proteins.

The present methods of analysis of calcium, based mostly on the Kramer and Tisdall procedure,⁴ determine the total amount of calcium in the blood serum and do not differentiate between the physiologic states of the various fractions. Fluctuations in the diffusible and nondiffusible calcium fractions can occur in such a manner that they are not revealed by the analysis of the total amount of calcium, and therein lies a probable explanation for the discrepancies between laboratory and clinical observations in numerous instances of juvenile and para-

⁴ Kramer, B., and Tisdall, F. F. Clinical Method for Quantitative Determination of Calcium and Magnesium in Small Amounts of Serum and Plasma, *Bull. Johns Hopkins Hosp.* **32**: 44 (Feb.) 1921. Tisdall, F. F. A Note on the Kramer-Tisdall Method for the Determination of Calcium in Small Amounts of Serum, *J. Biol. Chem.* **56**: 439 (June) 1923.

thyroid tetany. Thus Liu⁵ found that tetany may exist when the total amount of calcium in the serum is as high as 9 mg per hundred cubic centimeters, and latent tetany may be present even when the total amount of calcium in the serum is as high as 10.2 mg per hundred cubic centimeters. Our observations in parathyroid infantile tetany (table 1) confirm those of Liu and show that manifest and latent tetany can be present when the values for calcium in the serum are within the normal limits of variation. Figures for the total amount of calcium in the serum lying within the normal limits of variation, when symptoms of tetany were present, have not been an uncommon observation at the University of California Hospital.

The ideal diagnostic method for tetany by chemical means would be a procedure for measuring the amount of physiologically available calcium that is effective in the maintenance of the normal neuromuscular irritability. But here one is confronted with the difficult problem of what constitutes the physiologically available calcium. The work of Loeb,⁶ Ringer,⁷ and others pointed to the ionic calcium in the blood as being the best measure of physiologically available calcium for the control of neuromuscular irritability. Attempts at the determination of the ionic blood calcium have been made⁸ but all such proposed methods in their present state are clinically impracticable. An analytic procedure

5 Liu, S. H. Comparative Study of Effects of Various Treatments on Calcium and Phosphorus Metabolism in Tetany, Chronic Juvenile Tetany, *J Clin Investigation* **5** 259 (Feb) 1928, Chronic Adult Idiopathic Tetany, *ibid* **5** 277 (Feb) 1928.

6 Loeb, J. On Ion-Proteid Compounds and Their Rôle in the Mechanics of Life Phenomena, 1 The Poisonous Character of Pure NaCl Solution, *Am J Physiol* **3** 327, 1900, On an Apparently New Form of Muscular Irritability (Contact Irritability?) Produced by Solutions of Salts (Preferably Sodium Salts) Whose Anions Are Liable to Form Insoluble Calcium Compounds, *ibid* **5** 362, 1901.

7 Ringer, S. A Further Contribution Regarding the Influence of the Different Constituents of the Blood on the Contraction of the Heart, *J Physiol* **4** 2, 1883.

8 Neuhausen, B. S., and Marshall, E. K., Jr. Electrochemical Study of Condition of Several Electrolytes in Blood, *J Biol Chem* **53** 365 (Aug) 1922. Brinkman, R. Einige Bemerkungen über die Bedeutung des Blutkalks, *Biochem Ztschr* **95** 101, 1919. Trendelenburg, P. and Goebel, W. Tetanie nach Entfernung der Epithelkörperchen und Calcium Mangel im Blute, *Arch f exper Path u Pharmacol* **89** 171, 1921.

TABLE 1—*Observations in Parathyroid Infantile Tetany* *

Name	Calcium, Mg per 100 Cc			Inorganic Phos- phate, Mg per 100 Cc	Proteins, per Cent	
	Total	Dif- fusible	Nondif- fusible		Albu- min	Glob- ulin
I T						
						Twelve hours after convulsion, posi- tive signs of tetany present
8/25/28	63	32	30			
9/ 1/28	89	30	59			Convulsion preceded the taking of sample, signs of tetany present
10/10/28	90	30	60			Convulsion, signs of tetany present, sample taken after convulsion
6/ 6/29	85	42	43			Under treatment, subjective irrita- bility present, Chvostek sign doubt- ful, no outright signs of tetany present
K						
9/28/29	40					Reported from a reliable clinical lab- oratory, convulsion at time sample taken
9/29/29	72	37	35			Parathyroid extract Collip, 10 units, with calcium lactate by mouth 24 hours before sample was taken, subjective symptoms present
10/ 1/29	68	40	28			Medication was discontinued sample taken on appearance of first sub- jective symptoms, consisting of ful- ness in head and stiffness of the face
Baby W	102	32 41	70			Six weeks old, pneumonia, convul- sions, calcium chloride administered by intravenous route, dose 5 cc of 5 per cent solution for 5 days, cod liver oil by mouth, convulsions ceased after therapy, none at time second sample taken
Z	76	32	44	24		Osteomalacia, tetany, convulsion prior to taking of sample
Br	93	37	56			Man, aged 36, palpitation, tachycar- dia, tremor of hands, mild signs of hyperthyroidism, positive Hoffman sign, operation, microscope exami- nation showed lugolized hyperplasia of the thyroid gland, sample taken before operation
S *						Chvostek and Hoffman signs, posi- tive, patient very nervous, no con- vulsions
4/ 5/30	71	38	33	52	45	25
4/11/30	Viosterol 6 minimums per day by mouth					Patient showed subjective relief, Chvostek sign not obtained
4/17/30	89	45	44	45	42	26
4/17/30	Viosterol 45 minimums per day by mouth					Hoffman sign doubtful
5/ 7/30	72	35	37	47	39	16
						Relapse, very nervous, questionable convulsions
Baby L	109	55	54			Petit mal, calcium chloride adminis- tered intravenously, cod liver oil by mouth, convulsions continued, con- sisting of slight stiffening of legs and twitchings of one corner of mouth
Be	111	58	53			Isolated muscle cramps
Ma	106	54	52			Hysteria, carpopedal spasm
LaCl	101	55	46			Hysteria, carpopedal spasm and extension of extremities
Bro	95	42	53			Hysteria, carpopedal spasm stiffness of extremities, also pelvic inflam- matory disease

* All data are from the University of California hospitals except that from the medical service of Dr. Roland Cummings, the Los Angeles County General Hospital (It is to be noted that the patient relapsed under large doses of viosterol)

that is practicable for the clinical laboratory is the determination of the diffusible calcium fraction in the serum⁹ This fraction, although it is not completely ionized, contains the ionic calcium of the blood There are many observations to indicate that the diffusible calcium can be used as a measure of the state of the physiologically available calcium in the blood stream¹⁰

9 Cameron and Moorhouse (*J Biol Chem* **63** 687 [April] 1925) and recently Cantarow (*Calcium Studies Effect of Parathyroid Extract on Diffusibility of Calcium in Human Beings*, *Arch Int Med* **44** 834 [Dec] 1929) objected to the determination of the diffusible calcium by the methods of ultrafiltration or compensation dialysis on the ground that artificial membranes cannot give the same distribution of constituents as that given by the living membranes of the capillary walls in the animal body To avoid this objection, they proposed and used the calcium content of the spinal fluid as a measure of the true diffusible calcium in the blood Accordingly, the former authors, working on parathyroidectomized dogs, concluded that the nondiffusible calcium disappeared in tetany, and the latter worker concluded that an increase in the nondiffusible fraction was responsible for the rise in the total amount of calcium after the injection of parathyroid extract in man In each instance, they have arrived at conclusions opposite to the observations of the majority of observers employing ultrafiltration or compensation dialysis The validity of the results of the aforementioned authors rests on the correctness of the view that at all times the amount of calcium in the spinal fluid represents the actual value of the diffusible calcium in the blood The nondiffusible calcium in this work was obtained by subtracting the amount of calcium in the spinal fluid from the figures for the total amount of calcium in the serum If the alterations in the calcium in the spinal fluid do not parallel the changes of the diffusible calcium in the blood, both in time and magnitude, as must necessarily be the case if the establishment of equilibrium between the blood and the spinal fluid lags, then the amount of calcium in the spinal fluid cannot be used as an index of the condition of the diffusible calcium in the blood and the deductions drawn by the aforementioned authors are false One of us has recently presented evidence to show that the calcium in the spinal fluid is not continuously in equilibrium with that in the blood (Greenberg, D M, and Ballard, H A Comparison of the Diffusible Calcium of the Serum and the Calcium of the Spinal Fluid, *J Biol Chem Proceedings* **78** 65 [May] 1928 Greenberg, D M with the assistance of Ballard, H E, and Dalton, J B A Comparison of Ultrafilterable Serum Calcium and Cerebrospinal Fluid Calcium in Humans, *Proc Soc Exper Biol & Med* **27** 514, 1930), and this view is supported by the recent work of Hertz (*Biochem Ztschr* **217** 337 [Jan] 1930) The authors have further considered the objections against the employment of artificial membranes in another communication (Greenberg, D M, and Gunther, L *J Biol Chem* **85** 491 [Jan] 1930)

10 Stewart, C P, and Percival, G H Calcium Metabolism, *Physiol Rev* **8** 283 (July) 1928, *Studies in Calcium Metabolism Calcium Content of Corpuscles, Plasma, and Serum*, *Biochem J* **22** 548, 1928 Klinke, K Neuere Ergebnisse der Calcium forschung, *Ergebn d Physiol* **26** 235, 1928 Gunther, L, and Greenberg, D M The Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, *Arch Int Med* **45** 983 (June) 1930

The micromethod of ultrafiltration recently published by us¹¹ for the determination of the diffusible calcium in the blood serum offers a relatively simple practical method for the evaluation of the state of the calcium fractions in the blood and furnishes more useful data than can be obtained through the analyses of the total amount of calcium in the serum, plasma or whole blood. With this method, studies were made on parathyroid tetany, osteomalacia with tetany and tetany due to hyperventilation.

EXPERIMENTS ON PARATHYROID TETANY, JUVENILE TETANY AND OSTEOMALACIA WITH TETANY

Postoperative tetany developed in three patients, two women and one man who had undergone operations for subtotal removal of the thyroid gland. The detailed history of one case follows:

History—I F, an Italian woman, aged 33, entered the University of California Hospital on Feb. 1, 1926, complaining of an enlarged thyroid gland, prominence of the eyes, rapid pulse rate and palpitation of the heart. Twenty-three months prior to admission, she had been operated on in Switzerland because of these symptoms and signs. At the University of California Hospital, the diagnosis of multiple recurrent adenoma of the thyroid was made. The patient was operated on a second time on Feb. 13, 1926, in the surgical service, at which time a bilateral subtotal thyroidectomy was performed. On the day following the operation severe signs of tetany developed, as shown by the presence of carpopedal spasm and a bilaterally positive Chvostek sign. A diagnosis of postoperative parathyroid tetany was made. The total amount of calcium in the blood was 71 mg. per hundred cubic centimeters. The increased neuromuscular irritability was controlled by the combined therapy of 50 units of parathyroid extract-Collip by subcutaneous administration and 5 cc. of a 10 per cent solution of calcium chloride given by the intravenous route every six hours. Calcium salts were also administered by mouth. Eleven days after the operation she was discharged to the outpatient department, quite well, with instructions to take 15 Gm. of calcium lactate daily by mouth. The total amount of calcium in the blood on the day before discharge was 17 mg. per hundred cubic centimeters of serum. However, two days after discharge, the patient was readmitted with symptoms of tetany as before. The total amount of calcium was 87 mg. per cubic centimeter. Parathyroid extract-Collip was again administered in large initial doses that were gradually decreased over a period of eleven days, when she was again discharged to the outpatient department with instructions to take 2 Gm. of calcium lactate by mouth three times daily. There was 93 mg. per hundred cubic centimeters of calcium in the blood. During the period that she was followed in the outpatient department, the total amount of calcium varied around 8 mg. per hundred cubic centimeters, without outspoken clinical signs of tetany developing.

About a year after the first attack of tetany, the patient went through a normal pregnancy, and a congenitally rachitic infant was delivered at another hospital. The child was artificially fed and lived six months. On Aug. 8, 1928, slightly less than two and one-half years after the onset of tetany, the patient was readmitted

¹¹ Greenberg D. M., and Gunther L. On Determination of Diffusible and Non-Diffusible Calcium, *J. Biol. Chem.* **85** 491 (Jan.) 1930.

to the University of California Hospital with symptoms of tetany, and the total amount of calcium was 67 mg per hundred cubic centimeters. Three months before this admission, a second child was born,¹² which she nursed. At the birth of the child she discontinued the large doses of calcium lactate (20 Gm daily) that she had been accustomed to taking.

On a therapeutic regimen consisting of large doses of calcium lactate administered by mouth in divided doses, viosterol administered orally and parathyroid extract-Collip given subcutaneously, the total amount of calcium in the blood rose to 95 mg per hundred cubic centimeters in eight days. The patient was again discharged on August 18, and seven days later she was readmitted with signs of tetany. Twenty units of parathyroid extract-Collip were administered subcutaneously that evening. The following morning the first specimen of blood was taken for study of the diffusible calcium. The signs of increased neuromuscular irritability were still present. The total amount of calcium was 63 mg per hundred cubic centimeters and the diffusible calcium was 3 mg per hundred cubic centimeters, the nondiffusible calcium by difference was 33 mg per hundred cubic centimeters. After the administration of 50 units of parathyroid extract-Collip, the outspoken signs of tetany diminished, but the patient remained in a hyperirritable state. A second attack of tetany occurred in the hospital three days after admission (September 1). An analysis of the total amount of calcium at this time showed a value of 89 mg per hundred cubic centimeters, the diffusible calcium was 3 mg and the nondiffusible calcium 59 mg per hundred cubic centimeters.¹³ One and one-half months later, after the patient's discharge, convulsions appeared again, and clinical signs of tetany were present. The blood for analyses of the fractional calcium was taken within twelve hours of the convulsions, and showed a total amount of calcium of 95 mg per hundred cubic centimeters, a diffusible calcium of 3 mg and a nondiffusible calcium of 65 mg per hundred cubic centimeters. When seen in the outpatient department, June 6, 1929, the patient seemed to be enjoying a fair degree of health, but she was still "nervous." At this time a physical examination showed that a questionable Chvostek sign was present. The analysis of the fractional calcium showed a total amount of calcium of 85 mg per hundred cubic centimeters, the diffusible calcium was 42 mg and the nondiffusible calcium 43 mg per hundred cubic centimeters. The clinical condition was interpreted as possibly being latent tetany.

COMMENT

The observations are summarized in table 1. It can be seen that in patient I F, in each instance, the diffusible calcium showed values between 3.3 and 3 mg per hundred cubic centimeters of serum shortly after the onset of clinical tetany. During the entire period of active clinical tetany, the nondiffusible calcium varied between 3 and 6.9 mg per hundred cubic centimeters. We have already noted that Cameron

12 After intensive treatment with cod liver oil, ultraviolet light and calcium, a sample of the child's blood at the age of 4 months showed a diffusible calcium of 4.3 mg per hundred cubic centimeters. As will be pointed out later, there is good reason to believe that the diffusible calcium level of the infant was much lower at an earlier date. Diagnosis of congenital rickets was also made.

13 In this instance, while the diffusible calcium was still low, the nondiffusible calcium is well within the normal range.

and Moorhouse¹⁴ arrived at the conclusion that in parathyropival tetany there is a reduction only in the nondiffusible calcium. This was also claimed by Cruickshank¹⁵ prior to Cameron and Moorhouse. If this contention is correct, the nondiffusible calcium should have dropped to low figures during these active states, whereas in reality, the analyses showed that the nondiffusible calcium was within normal limits in two of the three analyses¹⁶. In the first analysis on patient I F and in the analyses on patients K and S, the nondiffusible calcium also showed a decrease confirming the observations of von Meysenbug and McCann¹⁷ and Moritz¹⁸ that the nondiffusible as well as the diffusible calcium may show a decrease in tetany. But we cannot confirm their contention that the diffusible and nondiffusible calcium necessarily decrease in the same ratio. Our results are in conformity with those of Liu,⁵ who reported similarly low values for the diffusible calcium in chronic juvenile tetany regardless of the state of the nondiffusible calcium. Likewise in his cases, clinical improvement did not follow the increase in the nondiffusible fraction of the serum calcium, but did follow the increase in the diffusible fraction.

The nondiffusible calcium, qualitatively at least, depends on the amount of the serum proteins,¹⁹ and it may vary in such conditions as nephrosis without a concomitant variation in the diffusible calcium, as was first indirectly inferred by Salvesen and Linder²⁰ and recently by Peters and Eiserson²¹. We have observed in two cases of nephrosis at the University of California Hospital,²² a decrease in the total amount of

14 Cameron and Moorhouse (footnote 9)

15 Cruickshank, E W H. Studies in Experimental Tetany, Distribution of Calcium, Colloidal and Ionic Calcium, *Brit J Exper Path* **4** 213 (Aug) 1923

16 In normal persons we have found the extreme variation of between 41 and 74 mg per hundred cubic centimeters for nondiffusible calcium and from 42 to 68 mg per hundred cubic centimeters for diffusible calcium

17 von Meysenbug, R, and McCann, G F. Diffusible Calcium of Blood Serum, Human Rickets and Experimental Dog Tetany, *J Biol Chem* **47** 541 (Aug) 1921

18 Moritz, A R. Effect of Ultra-Violet Irradiation on State of Serum Calcium, *J Biol Chem* **64** 81 (May) 1925, The State of Serum Calcium in Experimental Hypo- and Hyper-Calcaemia, *ibid* **66** 343 (Dec) 1925

19 Marrack, J, and Thacker, G. State of Calcium in Body Fluids, *Biochem J* **20** 580, 1926. Loeb, R F, and Nichols, E G. Factors Influencing Diffusibility of Calcium in Human Blood Serum, *J Biol Chem* **72** 687 (April) 1927

20 Salvesen, H A, and Linder, G C. Inorganic Bases and Phosphates in Relation to Protein of Blood and Other Body Fluids in Bright's Disease and in Heart Failure, *J Biol Chem* **58** 617 (Dec) 1923, Relation Between Calcium and Protein of Serum in Tetany Due to Parathyroidectomy, *ibid* **58** 635 (Dec) 1923

21 Peters, J P, and Eiserson, Leo. The Influence of Protein and Inorganic Phosphorus on Serum Calcium, *J Biol Chem* **84** 155, 1929

22 This phenomenon, in nephrosis, has been further confirmed by one of us (L G) on further studies conducted on the Medical Services of Drs W H Leake and V R Mason at the Los Angeles County General Hospital

calcium, as a result of decrease in the nondiffusible calcium concomitant with low values for serum proteins. Liu has observed a decrease in the nondiffusible calcium for similar reasons in nephrosis and in kala-azar.²³ In these cases, as in cases of jaundice with low values for the total amount of calcium, in which there is also a decrease in the nondiffusible calcium,²⁴ no symptoms of tetany were observed. In the infant W, and in the adults with osteomalacia associated with tetany, at the time of convulsions, the diffusible calcium level was low, below 3.5 mg per hundred cubic centimeters similar to that seen in the parathyroid tetany in patients I, F, and S. The diffusible calcium in the infant rose to 4.1 mg per hundred cubic centimeters with alleviation of symptoms after five days of combined treatment with calcium chloride administered intravenously and cod liver oil administered by mouth. Liu⁵ has shown that the combined administration of cod liver oil and calcium salts is the most effective means for relieving the symptoms of tetany.

TABLE 2—Studies Conducted at the University of California Hospital on Six Patients with Hyperthyroidism Showing a Tendency Toward a Higher Value for Diffusible Calcium

Patient	Sex	Calcium, Mg per 100 Cc		Inorganic* Phosphate, Mg per 100 Cc	Serum Proteins, per Cent		Comment
		Total	Diffusible		Albumin	Globulin	
M	Male	10.2	6.1	3.9	3.9	2.2	Hyperplasia
S	Female	10.2	5.0	3.7	3.8	2.5	Hyperplasia
H	Male	10.2	5.2	5.0	4.0	1.9	Hyperplasia
W	Male	9.7	5.8	3.5	4.6	1.4	Adenoma
D	Male	10.5	5.8				Hyperplasia
T	Male	10.6	6.2				Hyperplasia

* All values in mg per hundred cubic centimeters of serum

In patient K, and likewise in patient S, the diffusible calcium estimated at the first appearance of subjective and objective symptoms, following the withdrawal of all treatment showed values of between 3.7 and 4 mg per hundred cubic centimeters. Patient B, who was suffering from mild hyperplasia of the thyroid, and who showed a positive Hoffman sign, also had a diffusible calcium of 3.7 mg per hundred cubic centimeters.²⁵ On the other hand in the group of patients with

²³ Liu, Shih-hao. Partition of Serum Calcium into Diffusible and Nondiffusible Portions, *Chinese J Physiol* **1**: 331 (July) 1927.

²⁴ Gunther, L, and Greenberg, D M. I. The Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, *Arch Int Med* **45**: 983 (June) 1930.

²⁵ A low value for diffusible calcium was not the usual observation in hyperplasia of the thyroid. Studies conducted on six patients at the University of California Hospital (table 2) showed a tendency toward the higher zone for the normal values. A low diffusible calcium is more apt to be seen following a subtotal thyroidectomy in patients who are apparently not entirely relieved of the symptoms of "nervousness" or increased neuromuscular irritability and tremor. This is further shown by case S, from studies conducted at the Los Angeles County General Hospital.

miscellaneous muscle cramps, including hysteria and petit mal and in the patients with tetany, J F and S, when they were clinically improved the diffusible calcium levels were definitely above 42 mg per hundred cubic centimeters

It is evident that in the control of the neuromuscular irritability in juvenile and parathyroid tetany in which presumably the ionic calcium is important, the alterations of the diffusible calcium fraction of the serum that contains the ionic fraction is the significant observation. Our results in agreement with those of Liu⁵ point to a value of about 35 mg per hundred cubic centimeters or less of diffusible calcium as being associated with active manifestations of tetany, while possibly values between 4 and 35 mg per hundred cubic centimeters may be associated with latent tetany.

The only recent work out of harmony with the conclusion that a low value for diffusible calcium is necessarily associated with the onset of tetany is that of Reed²⁶. Working on parathyroidectomized dogs, he arrived at the conclusion that no relationship can be established between the incidence and severity of tetany and either the absolute amount or the percentage of diffusible calcium, and that the characteristic feature of prolonged parathyroid deficiency is the tendency to instability of both the diffusible and nondiffusible calcium fractions²⁷.

Reed used the combined diffusion and ultrafiltration method of Moitz¹⁸ and we have elsewhere¹¹ pointed out that there is an element of doubt with this method because of the uncertainty that diffusion equilibrium is attained. Even so, a scrutiny of Reed's data shows that for three of his five dogs, namely, dogs 51, 52 and 56, the incidence and the severity of the tetany have a fairly high correlation with the drop in the value of the diffusible calcium. The data for the total amount of calcium presented by Reed bears out our contention that tetany may exist with values for the total amount of calcium remaining within the normal limits of variation.

TETANY DUE TO HYPERVENTILATION

It was pointed out in the introduction that attempts have been made to find either an alkaline shift in the acid-base balance or a lowering of the calcium ion concentration as the responsible factor in tetany, irrespec-

²⁶ Reed, C I. On State of Plasma Calcium in Parathyroidectomized Dogs, *J Biol Chem* **77** 547 (May) 1928.

²⁷ It may be pointed out that all work up to the present on the relation between the severity of tetany and the distribution of calcium in the blood suffers from the defect that no exact measure of muscular hyperirritability has been applied, so that statements made on the severity of the tetany can have only a qualitative significance. In the future quantitative measurements of such a property as the chronaxie will be required to determine more strictly the exact relations.

tive of the origin. Although claims have been made that there is an alkaline shift in the acid-base balance in infantile and parathyroid tetany,²⁸ the experiments of recent workers, employing the improved modern methods, show no alkaline shift in the blood reaction. As examples, we may cite the work of Drucker and Faber²⁹ and Suzuki³⁰. At the present time, the alkalosis theory of tetany in its application to tetany of juvenile and parathyroid origin may be considered to have been eliminated.

The theory that a reduction in the calcium ion concentration is responsible not only for infantile and parathyroid tetany, but also for tetany due to hyperventilation and an overdose of bicarbonate has become mainly associated with the names of Freudenberg and Gyorgy³¹. The essence of their theory is that increased alkalinity of the blood, increased inorganic blood phosphate or increased concentration of the bicarbonate ion produces a decrease in the ionic calcium without necessarily changing the total amount of calcium in the blood to any degree. This idea must further go back to the basis that the calcium ion concentration of the blood varies in accordance with some such formula as the Rona and Takahashi³² equation. From this equation

$$Ca = K \times \left[\frac{C_H}{C_{HCO_3}} \right]$$

in which Ca is the calcium ion concentration, C_H is the hydrogen ion concentration and C_{HCO_3} the bicarbonate ion concentration, it is seen that a decrease in the hydrogen ion or an increase in bicarbonate ion should result in a decrease in ionized calcium. However, it is to be noted that the Rona and Takahashi equation is derived on the basis that the blood calcium is always at its saturation value, and that the adjustment to equilibrium is rapid. If these postulates are not true, i. e., if the blood calcium is at a level below saturation or if supersaturation can persist for considerable periods, then the application of the Rona and Takahashi formula or other formulas based on the same hypotheses have

28 Lesne, E., Turpin, R., and Guillaumin, C. O. Sur quelques variations physico-cliniques du plasma au cours des états spasmodiques chez l'enfant, *Compt rend Acad d Sc* **179** 577, 1924. Cruickshank, E. W. H. Variations in Alkali Reserve and Acid-Base Balance in Tetany, *Proc Soc Exper Biol & Med* **21** 115, 1923. Wilson, D. W., Stearns, T., and Thurlow, M. P. The Acid-Base Equilibria in the Blood After Parathyroidectomy, *J Biol Chem* **23** 89 (Nov.) 1915.

29 Drucker, P., and Faber, F. Tetany, *J Biol Chem* **68** 57 (April) 1926.

30 Suzuki, Kohji. Experimental Study on Alkalosis, *Japan M World* **6** 108 (May) 1926.

31 Freudenberg, E., and Gyorgy, P. Relations Between Tetany and Rachitis, *Munchen med Wchnsch* **69** 422 (March 24) 1922, Tetany and Alkalosis, *Klin Wchnschr* **2** 1539 (Aug. 13) 1923.

32 Rona, P., and Takahashi, D. Beitrag zur Frage nach den Verhalten des Calciums in Serum, *Biochem Ztschr* **49** 370, 1913.

no validity. That the postulates on which the Rona and Takahashi equation is based are not valid is indicated by the work of Holt, La Mer and Chown³³ and Hastings, Murray and Sendroy³⁴ on the solubility of calcium salts in blood serum.

EXPERIMENTS

In considering how the calcium ion concentration of the blood might be reduced without a concomitant decrease in the total amount of calcium, the most reasonable view in tetany due to hyperventilation and an overdosage of bicarbonate is that as a result of the increased alkalinity the plasma proteins are able to combine with more of the calcium, forming unionized compounds. This would tend to keep the total amount of calcium high, even though the ionic calcium was being reduced. However, if this were true, a fractionating into the diffusible and non-diffusible calcium should show a decrease in diffusible calcium and an increase in nondiffusible calcium. To test this hypothesis, three experiments were carried out by us on tetany induced by voluntary hyperventilation. The results obtained are shown in table 3. The experiments were carried out on young normal adults, two females and one male, in much the same way as the similar experiments of Grant and Goldman.² A faster rate of breathing was employed than that used by Grant and Goldman, and tetany was thus induced in shorter periods of time.

The signs of tetany were observed in all three cases. Samples of the blood were drawn immediately before the experiment commenced and after definite symptoms of tetany were produced. The serum was analyzed for the total amount of carbon dioxide by the Van Slyke manometric method,³⁵ the p_H was determined by the Hastings-Sendroy colorimetric method,³⁶ and in a number of instances check determinations were carried out with the quinhydrone electrode. The total amount of calcium, diffusible calcium and inorganic phosphorus were determined by our previously described procedures.¹¹

Table 3 shows that there was a definite alkaline shift in the blood reaction in all cases amounting on the average to nearly 0.2 of a p_H

33 Holt, L. E., Jr., La Mer, V. K., and Chown, H. B. Studies in Calcification, Solubility Product of Secondary and Tertiary Calcium Phosphate Under Various Conditions, *J. Biol. Chem.* **64**: 509 (July) 1925.

34 Hastings, A. B., Murray, C. D., and Sendroy, J., Jr. Studies of Solubility of Calcium Salts. Solubility of Calcium Carbonate in Salt Solutions and Biological Fluids, *J. Biol. Chem.* **71**: 723 (Feb.) 1927.

35 Van Slyke, D. D., and Neill, J. M. Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J. Biol. Chem.* **61**: 523 (Sept.) 1924.

36 Hastings, A. B., and Sendroy, J., Jr. Studies of Acidosis, Colorimetric Determination of Blood p_H at Body Temperature Without Buffer Standards, *J. Biol. Chem.* **61**: 695 (Oct.) 1922.

unit We wish to emphasize, not the absolute values of the p_H but the relative shift As the determinations in any one experiment were carried out at the same time under identical conditions, the shift in the p_H must be considered valid in spite of the objections recently raised against the colorimetric methods of determining blood p_H ³⁷ As an additional safeguard, we obtained agreement within the limits of the readings between the colorimetric method and the quinhydrone electrode in many check tests

TABLE 3—Results Obtained in Experiments on Tetany Induced by Hyperventilation

Subject	CO ₂ Content, per Cent by Volume	Colorimetric p_H	Calcium, Mg per 100 Ce		Inorganic Phosphate, Mg per 100 Ce	Comment
			Total	Dif fusible		
B (female)						
Before hyper ventilation	56.5	7.53	9.85	5.70	3.70	Respiratory rate 36 per minute, symptoms: tightness across forehead and tingling in fingers and toes, spastic flexion of thumb and fingers of both hands, knee jerk reflexes hyperactive with increased spasticity of feet in extension, Chvostek sign negative
After 15 minutes hyperventilation	53.9	7.73	9.95	5.80	3.35	
T (female)						
Before hyper ventilation	62.0	7.45	10.6	5.35	4.85	Respiratory rate 40 per minute, symptoms: spastic flexion of thumb and fingers of both hands, knee jerk reflexes hyperactive with increased spasticity of legs, Trousseau sign positive, Chvostek sign negative, Babinski sign negative, headache developed at conclusion of experiment
After 10 minutes hyperventilation	60.0	7.57	10.8	5.20	4.80	
G (male)						
Before hyper ventilation	70.8	7.35	9.95	4.90	3.15	Respiratory rate 48 per minute, symptoms: tingling of fingers and tightness across forehead, spastic flexion of thumb and fingers of both hands, Trousseau positive, Chvostek sign slightly positive, Babinski sign negative
After 6 minutes hyperventilation	62.1	7.58	10.65	5.30	3.45	

The total amount of carbon dioxide in all cases shows a definite decrease. It is to be noted that, in conformity with other workers, we found a slight increase in the total amount of calcium, which probably may be attributed to a tendency toward dehydration in the blood. The significant observation is that the relation between the diffusible and non-diffusible calcium shows no alteration. The diffusible calcium is not at all decreased and even shows a slight increase. The experiments are definitely against the view that a reduction in the calcium ion concentration is a factor in tetany produced by an alkaline shift in the acid-base balance, namely, in tetany induced by hyperventilation and an over-dosage of bicarbonate.

37 Myers, V. C., and Muntwyler, E. Colorimetric Estimation of Hydrogen Ion Concentration of Blood, *J Biol Chem* 78:243 (June) 1928

SUMMARY

It has been pointed out that the analysis of the total amount of calcium in the serum is not a reliable guide to the state of muscular hyperirritability in juvenile and parathyroid tetany.

The determination of the diffusible calcium fraction in the serum offers a better criterion in such conditions. Our work and that of Liu point to a value of 3.5 mg. per hundred cubic centimeters or less of diffusible calcium as being associated with clinical symptoms of active tetany.

Tetany due to an alkaline shift in the acid-base balance, namely tetany due to hyperventilation and an overdosage of bicarbonate, shows no decrease in the diffusible calcium, and is therefore probably not associated with a lowering of the concentration of ionic calcium.

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CORRECTION

In the article by Dr. Francis C. Wood, Dr. Charles C. Wolferth and Mary M. Livezey, entitled, "Angina Pectoris: The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison with the Effects of Experimental Temporary Coronary Occlusion," which appeared in the March issue (*ARCH. INT. MED.* **47**: 339, 1931), Dr. Wood's address was given as New York. It should have been Philadelphia.

Book Reviews

ARTERIAL HYPERTENSION By EDWARD J. STIEGLITZ, M.S., M.D., Assistant Clinical Professor of Medicine, Rush Medical College, University of Chicago
Price, \$5.50 Pp 280, with 21 illustrations New York Paul B. Hoeber, Inc., 1930

This book on hypertension represents a peculiar mixture of good and bad. It fills a certain need by its comprehensive review of the physiologic, pathologic and clinical concepts established as a result of the classic studies of Janeway, Allbutt and others. It contains a complete bibliography for the most part, and this is well indexed. Most of the general problems of hypertension are adequately discussed, although the interest of the reader is often dulled by the ponderous diction, the forced analogies and the unnecessary repetition. Certain deficiencies and omissions are conspicuous. Thus, the pathology of the retinal changes and even the ophthalmoscopic observations are dealt with poorly. There is no chapter on experimental hypertension. The chapter on renal reserve contains an unusual amount of extraneous material, including an unclear and none too critical discussion of the theories of the formation of urine. The most serious difficulties, however, are encountered in the chapters on etiology, treatment and prognosis. Under etiology, the author lists almost everything in the past history of his patients, including the excessive consumption of Worcestershire sauce (page 59). Loose statements are found concerning the relation of thyrotoxicosis, the calcium content of the blood and focal infections to hypertension. Is it really true or demonstrable that "the etiologic importance of focal infection can hardly be over-emphasized" (page 69)? In discussing the treatment for hypertension by drugs, the author naively assumes that iodides can dissolve scars in blood vessels, thereby weakening them. He states that phenobarbital and bromides lowered the blood pressure in from 85 to 88 per cent of cases, but curiously omits the corresponding statistics for his own favorite drug, bismuth subnitrate (page 138). The chapter on prognosis illustrates how difficult it is for the medical mind to view therapeutic results without shutting the critical eye. In spite of these weaknesses, the book will be of considerable value to those interested in arterial hypertension. Since this is the first edition, there is opportunity for later improvement.

INSULIN THERAPY By E. FRANK, M.D., and A. WAGNER, M.D., Physicians of the Wenzel-Hancke Hospital, Breslau. Paper. Price, 8 marks. Pp 99. Leipzig Georg Thieme, 1930.

This little book opens with a concise historical sketch of the scientific work, from von Mehring and Minkowski to Banting and Collip, that led to the discovery and isolation of insulin. This is followed by a short discussion of the theories of the action of insulin and then by a practical exposition of the treatment for diabetes and its complications. Other chapters cover insulin therapy in the diabetes of children, resistance to insulin and complications attending the administration of insulin, especially the hypoglycemic reaction and edema caused by insulin. In a second section, critical consideration is given to the use of insulin in nondiabetic diseases, especially in cachexia and anorexia, in parenchymatous lesions of the liver, in hyperthyroidism, in infections and in other conditions. While the reviewer, from personal experience, is inclined to be somewhat more critical than the author as to the value of insulin in nondiabetic diseases, he nevertheless finds the book of great interest, and recommends it highly as a working guide for the use of insulin in diabetes and its complications.

NATURE OF THE SYMPTOMS ASSOCIATED WITH ESSENTIAL HYPERTENSION

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SOME PRESENT-DAY CONCEPTS OF THE SYMPTOMS

Two Groups of Symptoms—With the increasing evidence¹ for the view² that essential arterial hypertension occurs first and organic changes in the arterioles are a sequence, there has developed the belief that these apparently successive pathologic states are accompanied by separate groups of symptoms. These may be termed the early and the late group of symptoms, the former being associated with the stage of pure arterial hypertension and the latter developing as a result of the vascular changes. Rolleston expressed the belief that the early and late symptoms, which differ in character, differ also in etiology. It is important, therefore, for prognosis and study to distinguish between the so-called early and late symptoms. Sir Clifford Allbutt recognized this distinction, for, in his discussion of the symptom of dyspnea, he said that it "is a very late symptom. We are in the fifth act."⁴ Of similar prognostic significance are nocturia secondary to renal insufficiency, vertigo secondary to cerebral sclerosis, etc., symptoms that are accompanied and probably caused by widespread arteriolar disease. The early symptoms, however, are not accompanied by such diffuse vascular disease, but occur in patients in whom, after clinical, laboratory and

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From the Medical Clinic of the Boston Dispensary and the Division of Research

1 Moschcowitz, E. Hypertension with Minimal Renal Lesions, *J A M A* **77** 1075 (Oct 1) 1921. Bell, E T, and Clawson B I. Primary (Essential) Hypertension *Arch Path* **5** 939 (June) 1928. Kernohan, J W, Anderson E W and Keith, N M. The Arterioles in Cases of Hypertension *Arch Int Med* **44** 395 (Sept) 1929. Fishberg, A M. Anatomic Findings in Essential Hypertension, *Arch Int Med* **35** 650 (May) 1925. Evans, G. Causation of Diffuse Hyperplastic Sclerosis *Brit M J* **1** 548 (March 31) 1923.

2 Allbutt, C. Semle Plethora or High Arterial Pre sure in Elderly Persons *Tr Hunterian Soc* **77** 38, 1895-1896.

3 Rolleston H. High Blood Pressure from the Clinical Aspect, *Lancet* **2** 1203 (Dec 11) 1926.

4 Allbutt C. Diseases of the Arteries Including Angina Pectoris, London 1915, vol 1, p 381. vol 2, p 61.

postmortem study, no adequate pathologic evidence is revealed to explain the symptoms or the associated elevation in blood pressure⁵ The character and etiology of the early symptoms—headache, dizziness, weakness, fatigability, irritability, nervousness, etc—are the chief subjects of the present study These symptoms will be termed the early symptoms associated with essential hypertension⁶ It is not correct to speak of them as the early symptoms of essential hypertension, for (1) arterial hypertension itself is only a symptom,⁶ and (2) there is no evidence that the elevation in blood pressure produces these early symptoms

A group of premonitory signs and symptoms that precede the so-called early symptoms has been described by several investigators Alvarez⁷ and Cummings⁸ noted in young drafted men the frequent association of cyanosis of the extremities with elevated blood pressure However, the diagnosis of essential hypertension was not established definitely in their patients On the other hand, O'Hare, Walker and Vickers⁹ and Ohler¹⁰ studied the early life history of patients with long recognized primary hypertension They found a significant incidence of vasomotor symptoms, such as flushing, blushing, cold, sweaty and cyanotic hands, frequent epistaxis, abnormal flow at menstruation, migraine, fainting, dizzy spells and a type of personality characterized by morbid sensitiveness and a high-strung temperament O'Hare found that one or more of these symptoms were noted, usually about the second decade of life, by 42 per cent of 300 hypertensive patients, compared to 23 per cent of 436 patients used as controls Munk¹¹ stated the opinion that an increased excitability of the vascular system in the sense of a so-called sympathicotonia, or even a neurasthenic constitution, is commonly manifested in patients long before the arterial hypertension develops

5 Moschcowitz (footnote 1, first reference) Bell (footnote 1, second reference) MacCallum, W G Arteriosclerosis, *Physiol Rev* **2** 70, 1922 von Monakow, P Blutdrucksteigerung und Niere, *Deutsches Arch f klin Med* **133** 129 (Aug) 1920 Pal, J Ueber Herzhypertrophie und Hypertonie, *Med Klin* **15** 662 (July 6) 1919 Munzer, E Gefaess-Sklerosen, *Wien Arch f inn Med* **2** 1 (Dec) 1920

6 Rolleston (footnote 3) Christian, H A Discussion, *Am Heart J* **2** 688 (Aug) 1927

7 Alvarez, W C Surprising Frequency of Hypertension in a Group of Young Drafted Men, *California State J Med* **17** 367 (Oct) 1919

8 Cummings, R S Study of One Hundred and Fifty Cases of Hypertension, *California State J Med* **17** 373 (Oct) 1919

9 O'Hare, J P, Walker, W G, and Vickers, M G Heredity and Hypertension, *J A M A* **83** 27 (July 5) 1924

10 Ohler, W R The Signs and Symptoms of Hypertension, *Am Heart J* **2** 609 (Aug) 1927

11 Munk, F *Pathologie und Nierenkrankungen*, Berlin, Urban & Schwarzenberg, 1925, p 562

General Characteristics of the Symptoms—In addition to the conception of symptom groups, early and late, the understanding of the etiology necessitates a knowledge of the general character and distribution of the symptoms. There is widespread agreement in modern textbooks of medicine that the early symptoms are commonly "mistaken for manifestations of functional nervous disorders,"¹² and that "the general symptoms often lead to a diagnosis of neurasthenia."¹³ Allbutt¹⁴ said that "to distinguish in a particular case between hyperpiesia (essential hypertension) in its earlier stages and neurasthenia may be a matter of some difficulty." Riseman and Weiss¹⁴ also recently noted that in the psychoneuroses there are symptoms similar to those in arterial hypertension. It is also generally known that the early symptoms are referred to all parts of the body, so that no one symptom is typical of the disease. Kauffmann¹⁵ and Kylin,¹⁶ however, expressed the belief that the symptoms they most commonly encountered—dizziness, headache, palpitation, weight on the chest, rheumatoid pains, irritability, mild fatigue and sexual impotence—in their totality are typical of arterial hypertension even in its earliest stages, so that in many patients one may make the diagnosis merely on the history. The present study does not confirm this impression.

Previous Conceptions of the Etiology of the Early Symptoms—Finally, before presenting our own observations, three views concerning the etiology of the early symptoms will be discussed, having been selected because of their close adherence to the modern concept of essential hypertension.

One view is that the early symptoms are produced solely by the elevation in blood pressure. The evidence against this opinion may be summarized as follows: 1. There is apparently no close correlation between the onset, the number or severity of the symptoms and the level of the blood pressure. 2. The symptoms may frequently be relieved with little or no change in the level of the blood pressure.¹⁷ 3. Many

12 Goodridge, M. Essential Hypertension, in Cecil, R. L. Textbook of Medicine, Philadelphia, T. Nelson & Sons, 1927, p. 1090.

13 Mosenthal, H. O. Essential Hypertension, in Nelson. Loose Leaf Medicine, New York, Thomas Nelson & Sons, 1927, vol. 4, p. 515.

14 Riseman, J. E. J., and Weiss, S. The Symptomatology of Arterial Hypertension, *Am. J. M. Sc.* **180**:47 (July) 1930.

15 Kauffmann, F. Ueber die Häufigkeit einzelner wichtigerer Klagen und anamnestischer Angaben bei Kranken mit arterieller Hypertension, *München med. Wchnschr.* **71**:1230 (Sept. 5) 1924.

16 Kylin, E. Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926, pp. 65, 36 and 103.

17 Ayman, D. An Evaluation of Therapeutic Results in Essential Hypertension. *I. A. M. A.* **95**:246 (July 26) 1930.

hypertensive patients have no symptoms. In this regard, one should remember that different individuals vary in their susceptibility to stimuli,¹⁸ that which may produce severe headache in some people seems to have no effect on others. 4 Many similar symptoms occur in both arterial hypertension and arterial hypotension, so that they probably are not due to the increase or decrease of the blood pressure alone.³

The second concept considers both the symptoms and the elevation in blood pressure to be due to a toxemia.³ The belief that such a toxemia may be of bacterial origin is supported by the studies of Koessler, Lewis and Walker,¹⁹ who found in bacterial filtrates substances that, when injected into animals, caused a marked rise of blood pressure. The possibility of a metabolic toxemia has been shown by Major.²⁰ He observed that when methyl guanidine sulphate was injected intravenously into dogs, it produced a marked elevation of blood pressure. In the blood of hypertensive subjects, he found an increased amount of a substance that he believed to be guanidine.

The third hypothesis, as proposed by Pal,²¹ Kylin²² and Laufer,²³ is that the symptoms are caused by a primary disturbance of the vegetative nervous system, a disorder that they termed vegetative neurosis, angiotonic neurosis, etc. However, the authors of these terms did not state or imply that their so-called neurosis is of psychic origin. Kylin cited²² the following evidence: 1 There is a great variability in the blood pressure, which he said can be explained only as a nervous vasomotor disturbance and not as an organic contraction of the vessels. 2 The decreased tolerance for carbohydrates in essential hypertension suggests a disorder of the vagosympathetic system. 3 The marked reaction after the injection of epinephrine indicates a sensitiveness of the sympathetic nervous system. 4 The general symptoms of nervousness, so common in essential hypertension, cannot be distinguished from those of other nervous disorders.

18 Libman, E. Observations on Sensitiveness to Pain, *Tr. A. Am. Physicians* **41** 305, 1926.

19 Koessler, K. K., Lewis, J. H., and Walker, J. A. Pharmacodynamic Actions of Bacterial Poisons, *Arch. Int. Med.* **39** 188 (Feb.) 1927.

20 Major, R. H. The Possible Relationship Between Guanidine and High Blood Pressure, *Am. J. M. Sc.* **170** 228 (Aug.) 1925.

21 Pal, J. Arterieller Hochdruck, *Klin. Wchnschr.* **2** 1151 (June 18) 1923.

22 Kylin, E. Ueber die essentielle Hypertonie als Teilsymptom bei einer funktionellen Krankheit, *Acta med. Scandinav.* **59** 590, 1923.

23 Laufer, O. Ueber Subtonie (Lowenstein) nebst Bemerkungen über die Behandlung des arteriellen Hochdrucks, *Med. Klin.* **23** 1150 (July 29) 1927.

PRESENT STUDY

We have already noted the common statement of clinical investigators that the early symptoms associated with essential hypertension closely resemble those of the psychoneuroses. Because of this similarity, the problem of the relation of the symptoms presented by hypertensive patients to those observed in the psychoneuroses seemed worthy of study. The possibility of a psychic origin for the early symptoms associated with essential hypertension was suggested by the clinical experience of one of us (J. H. P.). This idea was further encouraged by an earlier study, in which¹⁷ 82 per cent of forty hypertensive patients were definitely relieved of their symptoms by suggestion. Added support for this opinion was afforded by the widespread belief that, as in the psychoneuroses, the greatest relief from the symptoms of which the hypertensive patients complain may be obtained by the removal of worries, fears and other disturbances in the psychic sphere.

The first step was to study separately the symptoms associated with essential hypertension and those of the psychoneuroses.

THE SYMPTOMS ASSOCIATED WITH ESSENTIAL HYPERTENSION

Method and Material—The data were obtained by (1) analyzing 100 unselected outpatient records of hypertensive cases, and (2) supplementing 53 of these records with a personal study of the patients. The 100 patients investigated had visited the clinic over periods ranging from one to seventeen years, while the known duration of their hypertension was from one to ten years. The minimal criteria²⁴ in this study for the diagnosis of essential hypertension were (1) many readings of the blood pressure of 160 mm. of mercury or more, and (2) the absence of evidence of nephritis on chemical and microscopic examination of the urine, normal dilution, concentration and phenolsulphonphthalein tests of the kidneys. There were 17 men, with an average age of 55, and a range in age between 42 and 70; there were 83 women with an average age of 52, and a range in age between 32 and 74.

Since there were 45 women in the age group of from 40 to 55 years, it might be contended that their symptoms were related to the menopause. The following facts make this idea improbable. 1. Of the fifty-three patients studied personally, there were twenty-five whose symptoms had begun before the age of 35 (chart 1), whereas the menopause occurs before 35 and after 55 in less than 0.7 per cent of women.²⁵ 2. Thirty-nine of the fifty-three patients had symptoms for

²⁴ Ayman, D. Normal Blood Pressure in Essential Hypertension, J. A. M. A. **94** 1214 (April 19) 1930.

²⁵ Graves, W. P. Gynecology, ed. 2, Philadelphia, W. B. Saunders Company, 1918, pp. 19, 22 and 128.

more than ten years (chart 1), whereas it is stated²⁵ that (a) the menopausal organic changes extend over a period ranging from several months to two years at the most, and (b) the average duration of symptoms after artificial menopause is from two to three months. 3 Most of the women patients gave no history of a recent or present menstrual disturbance. 4 There were identical symptoms in the hypertensive men of the same age group.

Frequency of Symptoms—The accompanying table shows the incidence of the symptoms in 100 patients with essential hypertension. These figures are derived not only from the symptoms complained of at the

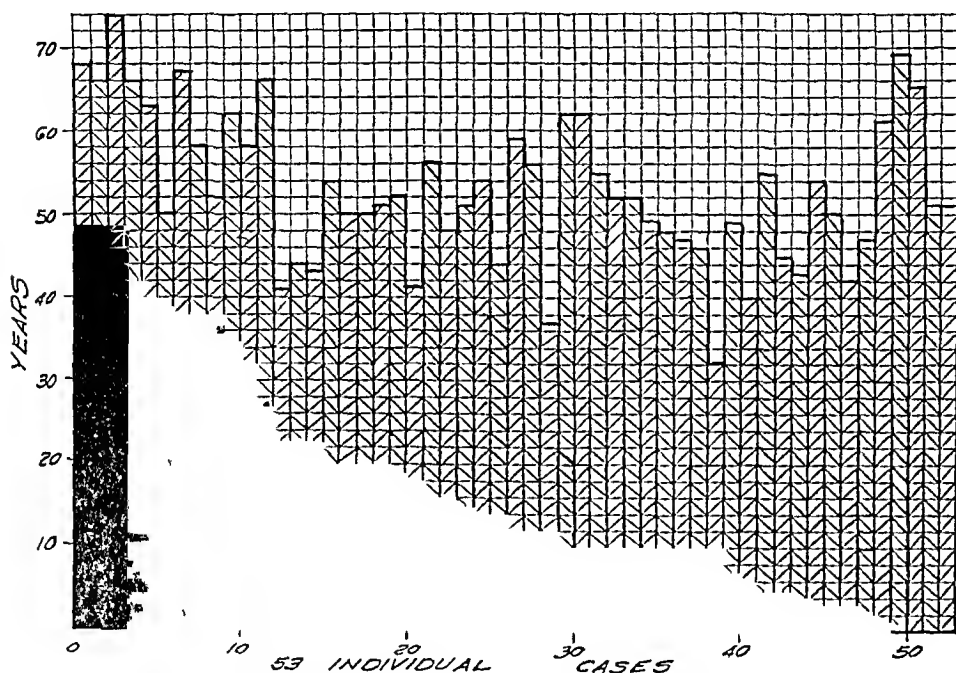


Chart 1—The individual duration of the symptoms in fifty-three hypertensive patients. Each vertical hatched column is to be considered continuous with a vertical black column directly below it. The total vertical height of each column (black plus hatched) represents the age of the individual patient. The individual vertical black column represents the duration of the symptoms in each case. For example, the first column represents a patient 68 years of age, whose symptoms have existed for forty-eight years, having commenced at the age of 20 years.

initial visit to the clinic, but from those which, in the recorded absence of demonstrable organic disease, were present previously or subsequently to the first visit. Hence our figures differ from the results of Kauffmann¹⁵ and Schultz and Biehn,²⁶ who apparently tabulated only

26 Schultz, J. H., and Biehn, W. Ueber die Häufigkeit einzelner wichtigerer Klagen und anamnestischer Angaben bei Kranken mit arterieller Hypertension, Deutsche med. Wchnschr. 51: 25 (Jan. 2) 1925.

the symptoms noted at the time of observation Our figures actually represent the totality of the symptoms in 100 patients that have occurred during the recognized span of the hypertension, or that can be shown by the history to have existed more or less continuously from an earlier time to the time of writing The symptoms utilized were not transitory, but lasted for days, weeks, months and years, and were often severe Chart 1, obtained in a manner similar to table 1, represents the total duration of the symptoms (present illness) in the fifty-three patients who were studied personally

General Characteristics—The accompanying table and chart 1 illustrate three general characteristics of "hypertensive" symptoms 1 These symptoms are usually multiple and widespread, being referred to almost

Frequency of Individual Symptoms in One Hundred Patients with Essential Hypertension

	Percentage		Percentage
Headache	72	Epigastric fulness	30
Pain	67	Anorexia	28
"Nervousness"	67	Heartburn	24
Dizziness	66	Nausea	21
Fatigue and weakness	65	Palpitation	18
Insomnia	63	Pain over cardiac area	15
Constipation	57	Vomiting	14
Fatigue	55	Tremors	12
Local or generalized flushing	54	Choking sensation	12
Weakness	38	Cough	9
Paresthesias	38	Unpleasant taste in the mouth	7
Eruetations of gas	37	Fainting	6
Shortness of breath	34	Loss of weight	6

every part of the body 2 There is a high frequency of certain symptoms, such as headache, pain, "nervousness," dizziness and fatigue 3 The duration of the symptoms (present illness) is unusually long Chart 1 shows the duration of the symptoms in the fifty-three patients who were studied personally Thirty-nine patients had symptoms over a period of more than ten years, twenty-six for more than fifteen years and ten for more than thirty-five years

That only 4 of the 100 patients were symptomless is probably due to the fact that in these patients the hypertension was found in the course of examination for other maladies

SYMPTOMS OF THE PSYCHONEUROSES

Most authorities agree that the psychoneuroses are psychogenic disorders²⁷ They arise from faulty adaptations to the difficulties of life There is a resultant emotional perturbation which expresses itself

²⁷ Ross, T A The Common Neuroses, New York, Longmans, Green & Company, 1924 Déjerine, J, and Gauckler, E The Psychoneuroses, Philadelphia, J B Lippincott Company, 1915

physically by symptoms. The development of the symptoms depends on the intensity and duration of the difficulties and on the individual susceptibility. Whereas a simple rebuke may cause brooding and headache in highly sensitive and susceptible persons, it requires great life and death conflicts, such as those in the front line trenches, to produce "shell-shock" psychoneuroses in others. There may then result a functional disorder of any mechanism, organ or region of the body.

The diagnosis rests on three facts: (1) The presence of symptoms, which are often multiple, widespread and usually not conforming in their entirety to any other clinical picture. With these are usually associated symptoms and signs of emotional instability such as irritability, inability to concentrate, excitability and attacks of weeping. (2) Negative results of a physical examination. (3) Elicitation from the patient of the fact that a period of important emotional stress preceded the development of symptoms. The diagnosis may be corroborated further by long clinical observation and psychotherapeutic success.

Methods and Data—The symptoms of psychoneurosis were studied in a group of fifty psychoneurotic patients, observed personally, who had been coming to the clinic for many years because of the somatic symptoms of neurasthenia, anxiety neurosis or hysteria. These patients, with normal blood pressure, were of the same age as the hypertensive patients. The average age was 48, with a range in age between 35 and 66. The data were obtained in the same way as in the hypertensive group. In twenty-four of the fifty, the onset of symptoms occurred before the age of 35 (chart 2). This fact, together with evidence similar to that already presented for the hypertensive group, makes unlikely a menopausal origin of the symptoms.

COMPARISON OF SYMPTOMS OF BOTH DISEASES

Chart 2 illustrates the duration of the symptoms in the fifty psychoneurotic patients. Twenty-nine of the fifty patients had their symptoms for ten years or more, eighteen for fifteen years or more and eight for twenty years or more. The close similarity in the duration of the symptoms in essential hypertension and in the psychoneuroses is strikingly apparent on comparison of charts 1 and 2.

In chart 3 the frequency, multiplicity and widespread distribution of the symptoms in the fifty psychoneurotic patients are illustrated by white hatched columns, and are compared with the same aspects of the symptoms in fifty patients with essential hypertension (black columns). Here again the striking agreement is evident.

However, this close similarity between the two diseases was found not to be limited to the general features of the symptoms, but to be

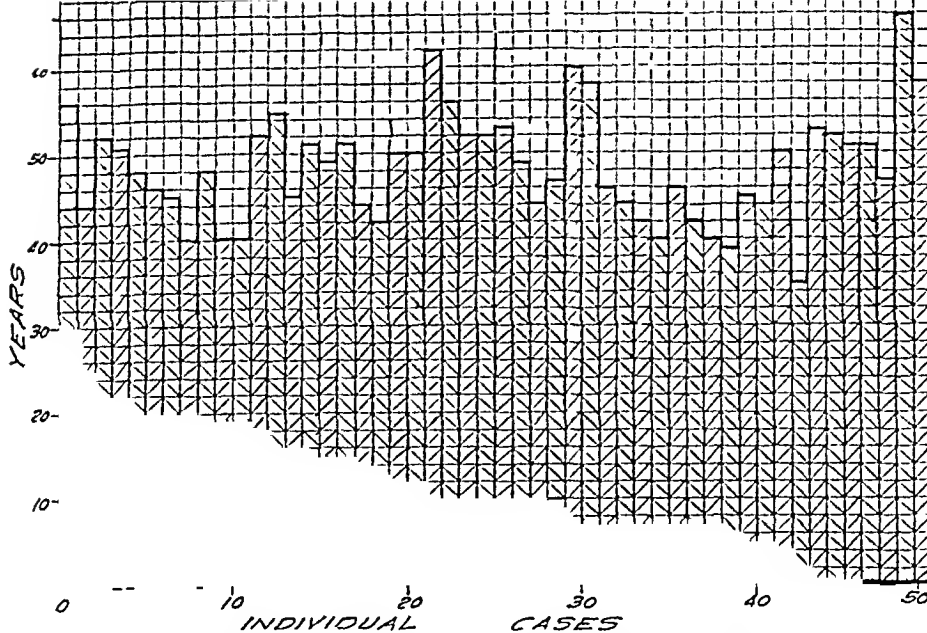


Chart 2—The individual duration of the symptoms in fifty psychoneurotic patients with normal blood pressure. The black and hatched columns are to be interpreted in the same way as in chart 1.

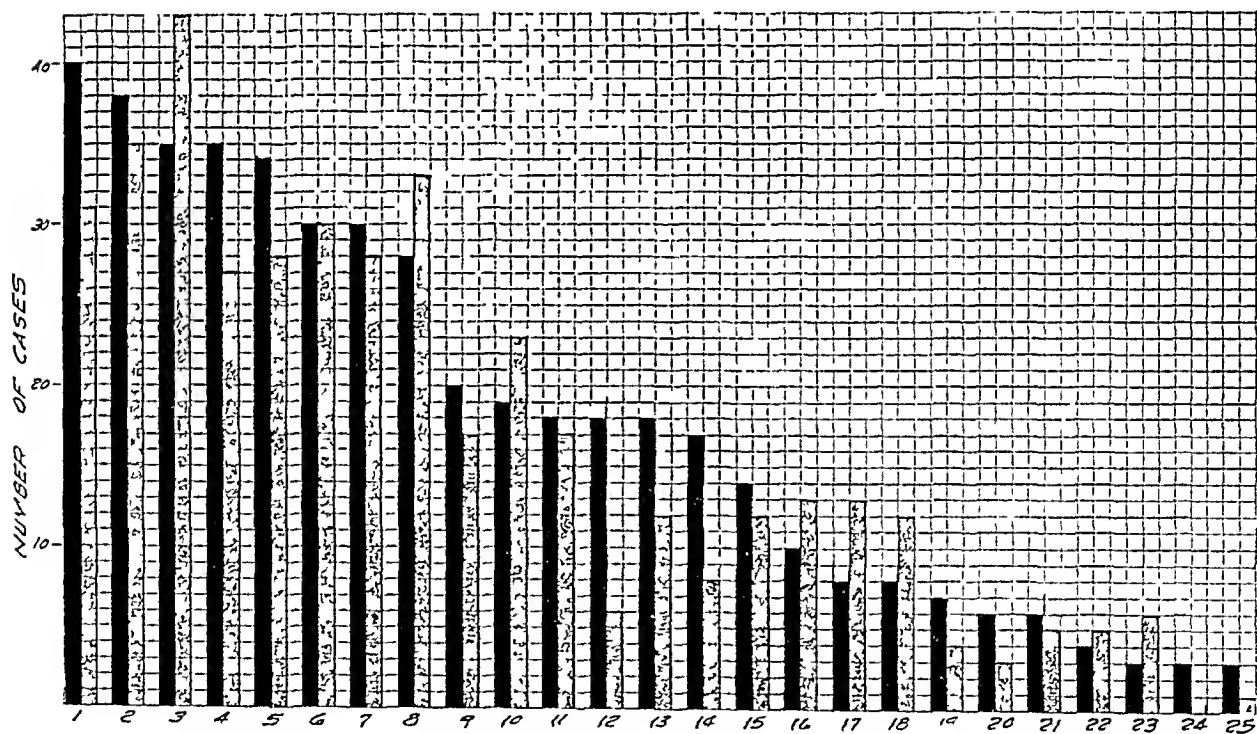


Chart 3—Comparison of the frequency of the individual symptoms in fifty patients with essential hypertension (black columns) and fifty patients with psychoneurosis (peppered columns). The columns labeled 1 represent the symptom irritability, and indicate that irritability was a complaint in forty of fifty hypertensive patients, while it was present in thirty-two of fifty psychoneurotic patients, column 2 represents headache, 3, pain, 4, dizziness, 5, insomnia, 6, fatigue, 7, local or generalized flushing, 8, constipation, 9, weakness, 10, paresthesias, 11, eructations of gas, 12, heartburn, 13, shortness of breath, 14, epigastric fulness, 15, anorexia, 16, nausea, 17, palpitation, 18, pain over cardiac area, 19, vomiting, 20, tremor, 21, choking sensation, 22, cough, 23, loss of weight, 24, fainting, and 25, unpleasant taste.

manifest in the character of the individual symptoms. For example, fatigability or a feeling of weakness was one of the most common symptoms encountered in the hypertensive group. Its usual intensity was so great that the patients frequently termed it "exhaustion." It was brought on by slight exertion or occurred when the patient was at rest, and frequently was not relieved by sleep. Its exact counterpart was regularly met with in the same frequency among the fifty psychoneurotic patients (chart 3). Fatigability, in fact, is one of the chief characteristics of the psychoneuroses. It is rarely found to such a degree in ambulatory patients with any other chronic disease, such as pulmonary tuberculosis. We shall also consider the symptoms headache and dizziness. We have been unable to find among the hypertensive patients a type of headache that might be termed characteristic, the patients described this symptom variously—as heaviness, emptiness, fullness, the feeling as if there were a band around the head, soreness, burning, throbbing, etc., occurring at any time of the day and in any part of the head. Dizziness was also described variously, from a feeling of light-headedness to true vertigo. The variability of the headaches and of the dizziness among our hypertensive patients is in conformity to what one sees in psychoneurotic persons²⁷. It should be pointed out that headache and dizziness occurred with slightly greater frequency among the hypertensive persons in our small series than among the psychoneurotic ones with normal blood pressure. The frequency is seen in chart 3. A similar comparison of all the other symptoms of the two diseases in the fifty patients showed a striking parallelism. The same symptoms occurred in both in about the same frequency.

THE EMOTIONAL LIVES OF HYPERTENSIVE PATIENTS

Even if the symptoms of both diseases have a marked likeness in their incidence and in their general and individual characteristics, it still remains to be shown that they have a common origin. Since the inception of the symptoms of the psychoneuroses is considered the result of a faulty adaptation to an emotional strain, and was so found in our fifty cases, it remained to investigate this possibility in the hypertensive group. This was studied in fifty-three hypertensive patients. A detailed history of the patients' emotional lives was recorded. It was found that many of them had experienced emotional disturbances resulting from faulty adaptation to marked psychic and environmental difficulties. These emotional burdens were found to extend back to youth in many patients and seemed to be of a magnitude surpassing those experienced by most normal persons. Roughly, personality studies of these patients showed that throughout their lives they responded with a marked emotional reaction to the usual incidents of life. In many cases, how-

ever, they had to face difficult situations. There seemed to be an abnormally high percentage of the patients who said they had had an "unhappy life." It was found, further, that the symptoms followed emotional difficulties. The following example illustrates briefly the type of emotional history obtained.

M. L., aged 41, a widow, whose blood pressure was 210 systolic and 110 diastolic, said that her life had been unhappy since the age of 13. She was averse to discussing the details of her life. At the age of 16 (1905), in Russia, her mother forced her to marry a man with whom she was hardly acquainted. He turned out to be a drunkard. They had three children, and then her husband deserted her. She took one of her children and went to England eighteen years before examination (1912), and while she was there she had a "nervous breakdown," the chief symptom of which was choking spells. Shortly afterward she left for the United States. She had never again seen her other two children, who lived with a wealthy brother in Russia. Her husband joined her again, but she was forced to leave him because of his abuse. The only child born in the United States had moved to a distant part of the country and had paid no attention to her. Her husband had died in an accident nine years previously, and she had no regrets. She had been living alone in a single room for seven years. (She cried often during the foregoing recital.)

Further analyses showed that not only did the original onset of symptoms in these hypertensive patients follow great emotional upsets, but in later life the recurrences of the symptoms were closely associated with periods of definite mental agitation, as illustrated in the following case.

The blood pressure of the patient had varied from 248 systolic and 120 diastolic to 180 systolic and 110 diastolic since she was first observed on Oct. 28, 1927. On March 7, 1929, the patient came to the clinic complaining of fatigue, inability to sleep and nervousness. She had been free from symptoms for a long period, but six weeks previously her present symptoms gradually developed and since had increased in intensity. Physical examination revealed no abnormality except the elevated blood pressure.

The patient's husband had been laid off from work six weeks previously, and their savings were so scanty that they were already in difficult financial straits. For the past four weeks he had been confined to the house by a cold. His irritability and continual presence at home disturbed the patient.

It is not meant that every hypertensive patient has had great emotional difficulties and an unhappy life. A few of our patients yielded no such information, whether because of reticence or not we do not know. In such patients it was often noted that they had no great sorrows or anxieties, but a life continually full of small annoyances. They seemed to be persons who worried about trivialities. They were frequently the ones with a family history of vascular disease. Here again it is to be noted that our cases were all dispensary cases, yet there

is a resemblance between this last group of patients and the type described by Moschcowitz,²⁸ which was met with in private practice

So far it may be summarized that the early symptoms associated with essential hypertension could not be differentiated from those of the psychoneuroses, either by their incidence or by their general and individual characteristics, that in both groups of patients no abnormality on physical or laboratory examinations could be found adequate to explain the symptoms, and, finally, that in both groups of patients a significant degree of maladjustment to emotional difficulties was found to explain the development of symptoms at the time they appeared

There is available, however, some added evidence that the early symptoms associated with essential hypertension are due not to organic changes, but to the emotional maladaptation of the patient. This evidence resides in the results of treatment. If the early symptoms associated with essential hypertension are of psychoneurotic nature, they should respond to three forms of therapy usually effective for the symptoms of psychoneurotic patients: (1) removal of environmental difficulties or adjustment to them, (2) sedatives and (3) suggestion. This has been found to hold true for our patients.

In regard to the removal of environmental difficulties or more adequate adaptation to them, it is probably the form of hypertensive therapy that has the most widespread support.²⁹

The successful use of sedatives in the symptomatic therapy for essential hypertension has also received wide mention.³⁰

Evidence for the successful effect of suggestion on "hypertensive" symptoms exists in an aforementioned investigation by one of us.¹⁷ In this study it was found that in 82 per cent definite symptomatic relief was obtained in a group of forty patients treated by simple suggestion, which consisted of prescribing a few drops of dilute hydrochloric acid daily. This impressively tasting medicine, undoubtedly nonspecific, coupled with continual encouragement, was used over periods of from one week to four months with a resultant success in 82 per cent. It

28 Moschcowitz, E. Hypertension. Its Significance, Relation to Arteriosclerosis and Nephritis and Etiology, *Am J M Sc* **158** 668 (Nov) 1919

29 Mosenthal, H. O. The Treatment of Essential Hypertension, *J A M A* **91** 698 (Sept 8) 1928. Fahrenkamp, K. Die psycho-physischen Wechselwirkungen bei den Hypertoniekrankungen, Stuttgart, Hippokrates, 1926. Goldscheider, A. Ueber Wesen und Behandlung der Hypertension des Blutdrucks, *Ztschr f ärztl Fortbild* **23** 1 (Jan) 1926

30 O'Hare, J. P. Treatment of Hypertension, *Am Heart J* **2** 510 (June) 1927. Henius, K. Brombehandlung bei Hypertonie, *Klin Wchnschr* **3** 958 (May 20) 1924

is only from such a point of view that one can interpret many of the last decade's 200 or more successes¹⁷ in the therapy for essential hypertension

While it seems reasonable to conclude that the early symptoms associated with essential hypertension are probably of psychic origin, the fundamental mechanism is not clear. Constitutional influences, endocrine products and possibly other factors may contribute to lessen the hypertensive patient's psychic and physical capacity for withstanding the stress and strain of life

SUMMARY

Clinical observations are presented to support the view that the early symptoms associated with essential hypertension are of psychic origin

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THE GAIN IN BODY WEIGHT ASSOCIATED WITH REMISSIONS IN PERNICIOUS ANEMIA¹

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In 1927, Minot and Murphy¹ drew attention to the striking gain in body weight observed in patients with addisonian pernicious anemia who were given liver therapy, and this observation has been borne out by the majority of subsequent reports. This gain in weight occurs whether whole liver or liver extract is used. Meulengracht and Holm² recently analyzed a series of thirty-six cases, with special reference to the gain in body weight, and showed that the average gain over a period of from one to two years was 54 pounds (24.5 Kg), showing no appreciable difference in patients receiving extract or whole liver or a combination of the two. I³ reported the case of one patient treated with whole liver who gained as much as 20 pounds (9 Kg) in one month. Wyckoff and Bloomfield⁴ cited the cases of two patients who were given extract only, and who gained 13.5 and 91 pounds (6.3 and 41.3 Kg) respectively.

There is a tendency to consider that this gain in weight is dependent on the action of the liver or of the liver extract itself rather than on the improvement in the blood and the general condition of the patient. However, in 1920, Minot,⁵ reviewing the symptomatology of pernicious anemia, stated that "loss of weight not infrequently occurs with relapses, to be regained in remissions," and quoted the case of a man weighing 180 pounds (81.6 Kg), who in a series of relapses lost between 35 and 50 pounds (15 and 22 Kg) on each occasion, gaining back his original weight during a remission. Such a gain of approximately 50 pounds is in striking accord with the average figure already quoted from Meulengracht's series of cases in which treatment with liver was used.

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1 Minot, G R, and Murphy, W P. A Diet Rich in Liver in the Treatment of Pernicious Anemia with Liver or an Effective Fraction of Liver. Study of 105 Cases, *J A M A* **89** 759 (Sept 3) 1927

2 Meulengracht, E, and Holm, S. Vegtførøgelsen ved leverbehandling af pernicious anæmie, *Ugeskr f læger* **91** 479 (June 6) 1929

3 Vaughan, J M. The Liver Treatment of Anemias, *Quart J Med* **23** 213 (Jan) 1930

4 Wyckoff, H A, and Bloomfield, A L. Liver Extract in Pernicious Anemia, *California & West Med* **30** 225, 1929

5 Minot, G R. Clinical Discussion of the Anemias, *Oxford Medicine*, New York, Oxford University Press, 1920, vol 2

It would appear, therefore, that liver per se, cannot be considered to exert any peculiar effect on the weight of patients with addisonian pernicious anemia, since equally striking changes were observed before its introduction as a therapeutic agent. Such changes occur coincident with an improvement in the blood picture, independent of the exciting cause of a remission.

The following factors might on theoretical grounds be responsible for the increase in body weight: (1) increased caloric intake dependent on the improved appetite, (2) retention of fluid leading to edema and (3) some alteration in metabolism similar to that occurring in myxedema.

The object of the present investigation was to determine as far as possible if one or more of these factors were involved.

METHODS

Twelve cases of addisonian pernicious anemia were followed during the last year. They showed no severe renal damage, as evidenced by the absence of albumin and casts from the urine and a blood pressure within normal limits. The patients were also being studied for special purposes unconnected with the present inquiry. They were given liver preparations by intravenous administration, as recently reported by Cohn, McMeekin and Minot,⁶ or digestion mixtures of beef-steak and gastric juice, as described by Castle and his associates,⁷ to initiate a remission. Improvement was then maintained by commercial extract.

To determine how far the caloric intake was of importance, daily records were kept of the exact value of the food taken. The diets were low in protein, as no red meat was given, in order to insure that the effect of any treatment should be uncomplicated by improvement possibly due to the ingestion of such meat. In calculating the value of the protein in any diet, allowances were made for the amount fed in the digestion mixtures. In all patients, therefore, except 1 and 12, the daily intake of protein did not exceed 50 Gm., the average being 42 Gm.

Seven patients received a strict basal diet, allowing 25 calories per kilogram of body weight. Two patients were given a diet well above their caloric requirements. Three patients received first a basal ration, and when after several weeks they showed no gain in weight in spite of improvement in the blood picture, they were given one of higher caloric value during the subsequent period.

In order to ascertain whether the retention of fluid might be responsible for the gain in weight, records were kept of the total excretion of urine and intake of fluid during twenty-four hour periods. It is recognized that such determinations

6 Cohn, E. J., McMeekin, T. L., and Minot, G. R. The Nature of the Material Effective in Pernicious Anemia, *J. Biol. Chem.* **87**: 49 (June) 1930.

7 Castle, W. B., and Locke, E. A. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *J. Clin. Investigation* **6**: 2 (Aug.) 1928. Castle, W. B. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. I. The Effect of the Administration to Patients With Pernicious Anemia of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, *Am. J. M. Sc.* **178**: 748 (Dec.) 1929. Castle, W. B., and Townsend, W. C. II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Human Gastric Juice, *ibid.*, p. 764.

are subject to considerable error, as DuBois⁸ pointed out, but it was thought that they might give some indication as to whether any considerable quantity of fluid was retained at any time and provide at least comparative figures

Determinations of the basal metabolic rate were made at intervals, a Benedict-Roth recording apparatus being used

RELATION OF GAIN IN WEIGHT TO CALORIC INTAKE

Table 1 shows the relation of the caloric intake to the gain in weight and total red blood cell count in twelve cases of pernicious anemia. Only

TABLE 1—*Relation of Changes in Body Weight to Caloric Intake, Red Blood Cell Count and Treatment*

Patient	Gain or Loss of Body Weight in Pounds After Treatment			Red Blood Cell Count in Millions per C Mm			Treatment
	Basal Diet* from 4 to 13 Weeks	Ample Diet* from 3 to 5 Weeks	From 2 to 24 Weeks After Leaving Hospital*	Before Treatment	On Leaving Hospital from 2 to 15 Weeks After Beginning Treatment*	From 2 to 24 Weeks After Leaving Hospital	
1	-9.75		-4.0	14	30	36	Digestion mixture, commercial extract
2	-3.0		-3.0	16	31	44	Preparation given intravenously, commercial extract
3	-3.0		+8.0	26	35	42	Preparation given intravenously, commercial extract
4	-0.5		+5.5	13	26	41	Preparation given intravenously, commercial extract
5	-2.0		+4.5	12	29	47	Digestion mixture, commercial extract
6	-7.0			26	39	47	Digestion mixture, commercial extract
7	+2.5		+4.0	19	27	47	Digestion mixture, commercial extract
8†		+3.00		21	44		Digestion mixture, commercial extract
9	-3.5	-0.75	+7.0	17	46	44	Digestion mixture, commercial extract
10	-2.75	+0.75	+4.5	26	39	47	Commercial extract
11		+10.25	+18.5	14	38	47	Digestion mixture, commercial extract
12		+4.25	+7.0	11	33	41	Digestion mixture, commercial extract

* The periods of time must not be regarded as those normally required to achieve the degree of improvement noted either in weight or in total red cell count, since the majority of the patients were being studied for special purposes. The materials tested varied considerably in potency, and the treatment was not always continuous.

† Too ill to weigh on entry.

one of seven patients on a strict basal diet, when he left the hospital, showed a gain over his weight before treatment. Six patients had a loss of weight varying from 9.75 to 0.5 pounds (from 4.4 to 0.2 Kg). Three patients who received first a basal and then an increased diet showed an increase in weight on the latter above that on the basal diet. Two patients who had had a diet above their caloric requirements through-

⁸ DuBois, E. A. *Metabolism in Health and Disease*, Philadelphia, Lea & Febiger, 1924.

out treatment showed a definite gain in weight 10.25 pounds (4.7 Kg) in patient 11, in thirty-four days, and 4.25 pounds (2 Kg) in patient 12 in eight days. The caloric intake in the first of these patients is difficult to calculate accurately, as he had difficulty in retaining all the beefsteak mixture fed by nasal tube. The daily excess over his basal requirements was approximately 700 calories. Patient 12 did not vomit, and his excess intake was approximately 1,000 calories. Therefore, four of five patients gained weight on an ample diet as opposed to the gain in weight of one of seven patients on a basal diet.

A more careful analysis of the weight during treatment is made in table 2, and shows that an almost constant fluctuation occurs in the body weight of the patient with pernicious anemia during a remission. This fluctuation is closely associated with changes in the red blood cells and,

TABLE 2—*Relation of Changes in Body Weight to Intake of Fluid and Output of Urine*

Patient	Gain or Loss of Body Weight in Pounds				Daily Average Gain or Loss of Body Fluid in Cc			Edema
	At Time of Reticulo- cyte Rise	Following Reticulo- cyte Rise	At Time of Discharge from Hospital	From 2 to 24 Weeks After Discharge from Hospital	Period I at Time of Reticulo- cyte Rise	Period II Following Reticulo- cyte Rise	Period III During Second Gain in Weight	
1	+7 25	-18 25	+1 25	+5 75	+670	+458	+369	+
2	+2 75	-5 75	No change	No change	+ 62	-353		Not noted
3	-2 0	-5 5	+ 4 5	+11 0	Record not complete			Not noted
4	+4 0	-7 5	+ 3 0	+ 6 0	+598	+ 67	+180	+
5	+4 5	-7 0	+ 0 5	+ 6 5	Record not complete			Not noted
6	-1 5	-7 0	+ 1 5		+249	-169		+
7	+4 0	-3 0	+ 1 5	+ 1 5	+557	-344	-193	+
8		-5 0	+ 8 0		+250	- 82	-294	Not noted
9	No change	-5 5	+ 4 25	+ 8 25	-463	-151	-202	Not noted
10		-2 75	+ 3 5	+ 3 75		-186		Not noted
11	+1 0	Weight rose steadily	+ 9 25	+ 8 25	+ 60		-102	Not noted
12	+8 0	- 5 0	+ 1 25	+ 2 75	+255	-390	- 40	+

as will be shown later, with alterations in the fluid balance. It naturally divides the time of recovery into three distinct periods. In the first period, lasting from the onset of treatment to the peak of the reticulocyte response, there was a gain in weight in seven of the ten cases in which the records were complete. The maximum gain was 7.25 pounds (3.3 Kg) in patient 1, who was receiving a basal diet at this time. Two patients showed a slight loss of weight, and in one the weight remained constant.

The second period occurred during the days following the peak of the reticulocyte rise. It was characterized by a loss of weight of from 18.25 to 2.75 pounds (from 8.3 to 1.2 Kg), occurring in all patients except patient 11, who was receiving an ample diet. The weight started to fall immediately after the peak of the rise and continued to fall for a period varying from four to twenty-one days.

During the third period there was a gain in weight in all patients except patient 2, whose weight remained constant. With one exception, however, the gain in weight in the patients receiving a basal diet, calculated from the original weight before treatment, did not exceed this level. In patients 9 and 10 the gain in weight occurred only after the basal diet had been increased. These observations, together with the fact that all except two patients gained weight in the weeks following their discharge from the hospital, when presumably they led more normal lives with no control exerted on their diet, suggest that caloric intake plays an important rôle in the gain in weight.

It has been suggested⁹ that the effect of certain liver extracts in lowering the blood sugar, as described by Murphy and Blotner,¹⁰ may account in part for the increased caloric intake through increasing appetite. Riddle,¹¹ however, stated that the fall in the level of the blood sugar during fasting is dependent on the metabolic adjustment accompanying remission rather than on the direct influence of liver or of liver extract on the level of the blood sugar. The one case he reported in which observations were made during a spontaneous remission showed 91 mg of sugar per hundred cubic centimeters as its lowest figure, which is hardly sufficient to account for a very appreciable increase in appetite.

It has also been suggested that the high content of vitamin B in both liver and certain liver extracts may contribute to the improved appetite and, therefore, to the increased caloric intake.

Since, however, improved appetite and gain in weight occur in spontaneous remissions, it seems unlikely that vitamin B is responsible for such changes.

RELATION OF GAIN IN WEIGHT TO INTAKE OF FLUID AND OUTPUT OF URINE

The analysis of the relation of intake of fluid and output of urine to gain in weight, which is made in table 2, shows, however, that possibly retention of fluid may play a part in the fluctuations observed in the weight during a remission. Variations in the fluid balance are seen to occur in the same periods as do alterations in body weight.

In the first period, all patients in whom the records were complete, except patient 9, who alone did not gain weight, showed an average daily excess of intake of fluid over output of urine. In three patients gross

9 Minot, G. R. The Treatment of Pernicious Anemia with Liver or with an Effective Fraction of Liver, *Tr. A. Am. Physicians* **49** 144, 1927.

10 Murphy, W. P., and Blotner, H. The Effect of Liver Feeding on the Blood Sugar, *J. Clin. Investigation* **4** 440 (Aug.) 1927.

11 Riddle, M. C. The Blood Sugar During Remission in Pernicious Anemia, *Ann. Int. Med.* **3** 1097 (May) 1930.

edema developed at this time, and in two others edema present at the time of admission became worse

During the second period, the output of urine exceeded the intake of fluids in seven of nine patients. There was, therefore, a complete reversal of the fluid balance associated with a similar reversal in body weight. The edema during this period decreased rapidly.

In the third period, when all patients gained weight, the fluid output still exceeded the fluid intake except in patients 1 and 4, in whom the edema, however, continued to decrease.

It is recognized that the measurement of the intake and output of fluid as an indication of the retention of water by the body is unsatisfactory. No stress is laid on the actual figures here recorded, but the association of gross edema with the period of apparent retention of water and its diminution or complete disappearance during the second period suggest that there is considerable significance in the results obtained.

Characteristic changes in the excretion of water have long been recognized in pernicious anemia. Cabot¹² noted edema in 69 per cent of his patients. Mosenthal,¹³ Stieglitz¹⁴ and Christian¹⁵ found a change in excretion as evidenced by a tendency to fixation of specific gravity without accompanying polyuria and a relative increase in the excretion of urine during the night. Saltzman¹⁶ also commented on the fixation of specific gravity. Meulengracht and his associates¹⁷ found that the inability to excrete large quantities of ingested fluid shown by a patient during a relapse is recovered during a remission. Kofanov¹⁸ more recently repeated and confirmed these results on patients receiving liver, but did not correlate his observations with the reticulocyte crisis. Such changes are reported not to occur in either chlorotic or posthemorrhagic anemias.

12 Cabot, R. C., in Osler and McCrae. *Modern Medicine*, Philadelphia, Lea & Febiger, 1927, vol. 5.

13 Mosenthal, H. O. Renal Function as Measured by the Elimination of Fluids, Salts and Nitrogen and the Specific Gravity of the Urine, *Arch. Int. Med.* **15** 733 (Nov.) 1915.

14 Stieglitz, E. J. Disturbances of Renal Function in Pernicious Anemia, *Arch. Int. Med.* **33** 58 (Jan.) 1924.

15 Christian, H. A. Renal Function in Pernicious Anemia, *Arch. Int. Med.* **18** 429 (Oct.) 1916.

16 Saltzman, F. Kliniska och patologisk-anatomiska iakttagelser rörande njurarnas förhållande vid den perniciosa anemien, *Finska lak-sällsk. handl.* **61** 157, 1919.

17 Meulengracht, E., Iversen, P., and Nakazawa, F. Pernicious Anemia. Edema and Reduction in Excretion of Water, *Arch. Int. Med.* **42** 425 (Sept.) 1928.

18 Kofanov, J. Beiträge zum Wasserstoffwechsel bei perniziöser Anämie, *Wien. Arch. f. inn. Med.* **19** 303, 1930.

Much discussion has arisen as to the cause of this disturbance in urinary excretion. Is the kidney itself at fault or are extrarenal factors responsible? Stieglitz¹⁴ and Saltzman¹⁶ emphasized the importance of anatomic lesions in the kidney, but the usual tests of renal function other than the excretion of water show little impairment. Albumin in the urine is not a constant feature. Cabot¹² reported a trace present in 40 per cent of his cases, while Meulengracht¹⁷ found it to be a transitory phenomenon only in 29 per cent of his cases. The excretion of thiosulphate was normal in the majority of Meulengracht's patients, and the same was found by Christian¹⁵ using phenolsulphonthalein. The evidence in respect to the retention of urea is contradictory. Gettler and Lindeman¹⁹ reported retention in 50 per cent of their cases, but they did not correlate their observations in any way with the age of the patient. Meulengracht,¹⁷ on the other hand, found it in only one of his patients, in whom cardiac decompensation was present. It would appear, therefore, that there is little evidence of severe renal damage while the albuminuria accompanying the edema of typical nephrosis is not found.

Essen and Porges²⁰ suggested that a deficiency of oxygen in the blood, dependent on the anemia, is responsible for the faulty functioning of the renal tissues. Meulengracht¹⁷ and Kofanov,¹⁸ however, showed that there is no disturbance of the excretion of water in either posthemorrhagic or chlorotic types of anemia, so that it is unlikely that the anemia itself, through its effect on the kidney, is responsible.

The questions of changes in the plasma proteins and colloidal osmotic pressure in the plasma have recently received attention. De Wesselow²¹ studied nine patients who were receiving liver therapy and found, as earlier observers, Kahn and Barsky,²² and Gettler and Lindeman¹⁹ had, done, that in severe stages of anemia there is a slight lowering of total plasma protein with a return to normal in the remission. He did not, however, consider the changes to be of significance. Meulengracht¹⁷ made comparative observations on the colloidal osmotic pressure in the plasma in nephrosis, in pernicious anemia and in secondary anemia. He found that although in some patients with pernicious anemia the pressure was lowered as much as that in the nephrotic patients, this reduction was dependent on quantitative rather than on qualitative changes. Furthermore, some cases of posthemorrhagic anemia had a similar lowering of colloidal osmotic pressure with no edema. There also

19 Gettler, A. O., and Lindeman, E. The Blood Chemistry of Pernicious Anemia, *Arch Int Med* **26** 453 (Oct.) 1920

20 Essen, H., and Porges, O. Ueber der Nierenfunktion bei Anämien, *Wien Arch f inn Med* **5** 195, 1923

21 deWesselow, O. L. V., and Barnforth, J. The Blood and Plasma Volume in Pernicious Anemia, *Lancet* **1** 1066 (May 26) 1930

22 Kahn, M., and Barsky, J. Studies of the Chemistry of Pernicious Anemia, *Arch Int Med* **23** 334 (March) 1919

appeared to be no constant parallelism between the amount of edema and the reduction in the excretion of fluids on the one hand and the lowering of colloidal osmotic pressure on the other. Though the lowering of plasma proteins may be a contributory cause of the edema present in pernicious anemia, it cannot alone be responsible.

It is possible that changes in the general metabolism of the body may be, in part at least, responsible for this retention of water. Newburgh²³ recently showed that pronounced changes in the balance between weight and water may be caused by varying the carbohydrate content of a diet in which the caloric value is kept constant, and also that considerable destruction of body tissues may be marked by the retention of water. It is known that certain profound changes do occur in the chemical constituents of the blood at the time of a remission. Muller²⁴ found that there is a rise in plasma cholesterol at this period, and Riddle²⁵ reported an increase in the uric acid, which rises and then falls, having the same relationship to the reticulocyte peak as does the intake of fluids. It is clear that careful and elaborate studies along the lines suggested by Newburgh²⁶ of a series of patients with pernicious anemia at the time of remission are required to enable one to determine the nature of the essential factors underlying the disturbance of the balance of water occurring at this time.

BASAL METABOLIC RATE

Observations on the basal metabolic rate in the present series of cases were not complete, but they agree with those of the majority of other observers in demonstrating that the improvement in the blood picture is associated with a return of the basal metabolic rate to normal or subnormal levels. Before the introduction of liver therapy, Meyer and DuBois,²⁷ Magnus-Levy,²⁸ Boothby and Sandiford,²⁹ and Becker³⁰

23 Newburgh, L. H., and Johnston, M. W. The Nature of Obesity, *J. Clin. Investigation* **8** 215 (Feb.) 1930.

24 Muller, G. L. The Relations of Cholesterol, Lecithin, Phosphorus and Fatty Acids to the Remission of Pernicious Anemia, *Am. J. M. Sc.* **179** 316 (March) 1930.

25 Riddle, M. C. The Endogenous Uric Acid Metabolism in Pernicious Anemia, *J. Clin. Investigation* **8** 69 (Dec.) 1929.

26 Newburgh, L. H., Johnston, M. W., and Falcon-Lesses, M. Measurement of Total Water Exchange, *J. Clin. Investigation* **8** 197 (Feb.) 1930.

27 Meyer, A. L., and DuBois, E. B. Clinical Calorimetry, XV, The Basal Metabolism in Pernicious Anemia, *Arch. Int. Med.* **17** 965 (June) 1916.

28 Magnus-Levy, A. Der Einfluss von Krankheiten auf den Energieaushalt im Ruhezustand, *Ztschr. f. klin. Med.* **60** 177, 1906.

29 Boothby, W. B., and Sandiford, I. Summary of the Basal Metabolism Data on 8,614 Subjects with Special Reference to the Normal Standards for the Estimation of the Basal Metabolic Rate, *J. Biol. Chem.* **54** 783 (Dec.) 1922.

30 Becker, G. Studien über den Stoffwechsel bei perniziöser Anämie, *Acta med. Scandinav.* **63** 478, 1925-1926.

reported a definite increase in metabolic rate during relapses, which returned to normal limits in the remissions. Tompkins, Brittingham and Drinker³¹ discussed a series of cases in which the level of the basal metabolic rate was either above or below normal during relapse, but in which during remissions, induced by transfusion, it returned to normal. Grassheim³² alone did not agree with this observation. Richards and Straus,³³ Alt,³⁴ and Bauer and Baldrige³⁵ made the same observations in cases in which the patients received either liver or liver extract. Alt claimed that the reticulocyte peak is accompanied by a rise in metabolic rate, but his figures are not convincing and are in disagreement with the extremely careful daily observations of Bauer and Baldrige. Three observations made on the cases in the present series at the time of the reticulocyte response showed no increase in metabolic rate.

SUMMARY

Correlation of the previous observations would seem to show that changes of the basal metabolic rate such as are found in myxedema are in no way responsible for the gain in weight occurring during a remission in pernicious anemia. Two factors would appear to be involved: (1) an initial retention of water and subsequent edema, which is transitory, the increase in weight at this period being due to increase in water, and (2) an increased caloric intake associated with the general improvement of the patient, the increase in weight now being due to increase in the body tissues.

None of the patients in the present series showed the startling gain in weight that has been reported in some instances. It is clear, therefore, that more prolonged and detailed observations are required before it is possible to determine whether or not the increased caloric intake alone is always sufficient to account for the increase in body weight. As far as the evidence can be judged at present it would appear, however, that caloric intake plays at least an important rôle.

31 Tompkins, E. A., Brittingham, H. H., and Drinker, C. K. The Basal Metabolism in Anemia with Special Reference to the Effects of Blood Transfusion on the Metabolism in Pernicious Anemia, *Arch. Int. Med.* **23**: 441 (April) 1919.

32 Grassheim, K. Stoffwechseluntersuchungen bei perniziöser Anämie, *Ztschr. f. klin. Med.* **111**: 601, 1929.

33 Richards, D. W., and Straus, M. L. Circulatory Adjustment in Anemia. *J. Clin. Investigation* **5**: 161 (Feb.) 1928.

34 Alt, H. L. The Metabolism in Pernicious Anemia, *Arch. Int. Med.* **43**: 488 (April) 1929.

35 Bauer, A., and Baldrige, C. W. The Effect of Liver Extract on the Basal Metabolic Rate in Pernicious Anemia, *Proc. Soc. Exper. Biol. & Med.* **26**: 872 (June) 1929.

CONCLUSIONS

1 Observations on the relation of gain in weight to caloric intake, fluid balance, basal metabolism and improvement in the red blood cell count have been made on twelve patients with pernicious anemia

2 Eleven patients showed an initial gain in weight irrespective of diet at the height of the reticulocyte rise, associated with retention of fluid and the appearance of gross edema

3 This initial gain in weight was followed by increased excretion of urine, disappearance or diminution of edema and loss of weight

4 A body weight exceeding that at the onset of treatment, with one exception, was found only in the patients receiving an ample diet

5 The improvement in the red cell count was associated with a return of the basal metabolic rate to normal or subnormal levels

6 The initial gain in weight associated with a remission in pernicious anemia would appear to be dependent on the retention of fluids, while increased caloric intake is, at least in part, responsible for the more prolonged gain in weight

THE AVERAGE DAILY ELIMINATION OF UROBILINOGEN IN HEALTH AND IN DISEASE, WITH SPECIAL REFERENCE TO PERNICIOUS ANEMIA

STANDARDIZATION OF METHOD BASED ON MESOBILIRUBINOGEN
(H FISCHER)*

C J WATSON, M D
MINNEAPOLIS

Relatively little use is made in clinical investigation of the considerable existing knowledge concerning the circulation and elimination of urobilinogen. This is not because of any general doubt about the significance of urobilin in the urine and feces, because the relationship of its concentration in these excreta to hepatic function, obstruction of the bile passages and destruction of the blood has been demonstrated repeatedly. Rather, the apathy in this regard may be attributed to the lack of any generally accepted method of quantitation and of exact knowledge concerning the daily output in health and disease. This report is the culmination of work begun three years ago, the purpose of which was to survey methods of estimation previously described in the literature and to use a method found to be reasonably accurate in ascertaining the average amount of urobilin eliminated per day in both normal and sick persons.

HISTORICAL REVIEW

Since the original description of urobilin by Jaffe, in 1868, an extensive literature has accumulated. The earlier publications were discussed in a review by Meyer-Betz in 1913. Wilbur and Addis, in 1914, with the description of their quantitative procedure, included a complete review of previously described methods. A fairly thorough critical discussion of the literature to 1920 may be found in Eppinger's book "Die Hepato-Lienalen Erkrankungen." These publications make unnecessary any exhaustive discussion of the literature, and in the following paragraphs only the more salient contributions will be considered. Following Jaffe's discovery of urobilin in the urine and bile, a similar pigment was observed in feces by Van Lair and Masius. Maly's hydrobilirubin, obtained by reduction of bilirubin, while later shown to be not identical with urobilinogen, nevertheless gave strong impetus to the enterogenous theory of formation of the urobilin, which

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was firmly supported by the clinical and experimental investigation of Mueller (This, in particular, consisted of the feeding of urobilin-free pig bile to a person with obstruction of the common duct whose stools and urine contained no urobilin, with its subsequent appearance in both) Le Nobel, in 1887, had given the name urobilinogen to the leuko-compound obtained by the reduction of bilirubin or urobilin. Sallet, ten years later, studied this chromogen intensively, and noted the ease with which it could be oxidized and that it was particularly sensitive to light. In 1903, Neubauer pointed out that the hitherto mysterious aldehyde reaction of Ehrlich, commonly occurring in pathologic urines, was due to the presence of urobilinogen. This reaction was employed by Charnas in a spectrophotometric method for the examination of urine and later of feces, and while criticism of this method in later years by Wilbur and Addis and Terwen is undoubtedly made with reason, the results obtained by its use, as published by Eppinger and Charnas, amply illustrate the value of such a procedure in clinical investigation. In 1911-1914, Hans Fischer and his associates afforded the most exact information yet obtained on the subject of chemical examination of urobilin. Stated as briefly as possible, this admirable work accomplished the following: (a) isolation of crystalline "hemibilirubin" following the reduction of bilirubin by sodium amalgam (so-called because yield was approximately 50 per cent), (b) isolation of crystalline urobilinogen from urine and crystallographic proof that hemibilirubin and urobilinogen are identical, (c) conclusive evidence that the previously described urobilins of Maly, and of Garrod and Hopkins, were mixtures, and that the hemopyrrol of Nencki and Zaleski is not the same as urinary urobilinogen.

As a result of this work, urobilinogen emerged as a definite substance while urobilin as yet has no identity. While urobilin is usually considered the oxidation product of urobilinogen, a chemical individual with urobilin characteristics has not been isolated by treatment of native urobilinogen or in vitro reduction products of bilirubin. On the contrary, Fischer was later able to show that the crystalline product in close relation with bilirubin, obtained by reduction of the latter, to which he gave the name mesobilirubin, was also in close relationship with hemibilirubin, or urobilinogen. This substance, however, failed to give the zinc fluorescence characteristic of urobilin. Fischer was induced to change the name of hemibilirubin to mesobilirubinogen because of its evident relationship to mesobilirubin and bilirubin. He was inclined to believe that what is ordinarily called urobilin is urobilinogen in relation with bile acids or cholesterol. Stercobilin was definitely shown to be a mixture. Because of the half yield in the reduction of bilirubin and because at first, all of the aldehyde reacting substance could not be removed from the urine with the one

procedure used, it was not possible to be sure that only one urobilinogen existed. A later method removed the substance quantitatively and, since it is identical with mesobilirubinogen, Fischer considered it to be probably the only urobilinogen. The constitution is that of a dibasic acid with four pyrrol nuclei (empirical formula, $C_{33}H_{44}N_4O_6$) and with one methin group, the latter responsible for the Ehrlich reaction.

Writers of articles on clinical medicine have given surprisingly little attention to these important observations in the description and discussion of methods. Eppinger considered it unfortunate that Fischer did not attempt the isolation of crystalline urobilinogen by application of his methods to feces directly rather than by the study of "stercobilin." Charnas, in 1913, described the isolation of crystalline urobilinogen from feces. This substance was found to differ in some respects from hemobilirubin; detailed characteristics and analyses were not given.

Eppinger's review, in 1920, contained a full discussion of the origin of urobilin and summed up the considerable evidence in favor of the enterogenous theory. In 1923, this sum total was increased by the work of Kammerer and Miller, who were able to produce urobilin *in vitro* by allowing bilirubin to remain in contact with feces under anaerobic conditions. Two years later the series of publications by Elman and McMaster, who employed the new technic of Rous and McMaster for sterile biliary fistula, offered convincing evidence of the enterogenous origin of urobilin in dogs. These investigators also demonstrated experimentally the enterohepatic circulation of urobilin and the consequent importance of urobilinuria in the study of the function of the liver. (Eppinger, from clinical observation of the duodenal contents, arrived at the belief that urobilin was rarely present in the normal bile and that the portion resorbed from the bowel must, under normal conditions, be entirely utilized by the liver, albeit in an unknown way.)

In the experiments of Elman and McMaster, urobilin promptly appeared in the urine with obstruction of the bile ducts to as little as one third of the parenchyma of the liver. The recent clinical observations of Wallace and Diamond are not in accord with this observation, with their method the amount of urobilin in the urine was not increased in extrahepatic obstruction of the bile duct, but was characteristic of injury to the parenchyma of the liver. In a recent study of tests for liver function, Piersol and Rothman stated the opinion that urobilinuria is the most delicate single evidence of derangement of the liver. Elman and McMaster also obtained evidence to show that urobilin may be formed in infected biliary passages with complete obstruction of the common duct. The urobilinuria, which occurred with increased destruction of the blood produced experimentally, was considered evidence of a simple excess in amount over that which the liver could excrete into

the bile This was not Fischer's opinion, since he found only a moderate amount of urine aldehyde reactions not comparable with those often seen in pathologic urines after feeding hemibilirubin to normal persons

Methods of quantitative estimation reported in the literature are numerous A complete review of these is found in the publication by Wilbur and Addis, in 1914, and again in Eppinger's "*Die Hepato-Lienalen Erkrankungen*," in 1920 Apart from the gravimetric method described by Hoppe-Seyler, the various methods have utilized either the fluorescence of urobilin with zinc salts or the urobilinogen aldehyde reaction or both, and these have been employed in colorimetric or dilution methods (the latter, either of color or absorption bands) The spectrophotometric method may be placed in the latter group This was first used by Gerhardt and Mueller, who accepted Vierordt's absorption value for Maly's hydrobilirubin Charnas was the first to employ the aldehyde reaction in a quantitative method, he also used the spectrophotometer His standard substance was obtained by the technic of Garrod and Hopkins As mentioned previously, this as well as the hydrobilirubin of Maly were shown by Fischer not to be chemical individuals Apart from this objection, two other features of Charnas' method have received unfavorable criticism In the method as applied to urines, a period of alkaline fermentation was allowed during which it was believed that any urobilin present was converted to urobilinogen In the experience of Wilbur and Addis, the opposite is true This feature was also criticized by Meyer-Betz and Terwen As regards Charnas' method for feces, Terwen has pointed out that loss of urobilinogen occurs when the alkaline extract is washed with ether Soon after the publication of the latter method by Eppinger and Charnas, in 1913, Brugsch and Retzlaff employed a modification of it to standardize a colorimetric method The values obtained with this method, so far as they can be compared, and also with a later modification of Charnas' method as described by Hueck and Brehme, in 1923, are lower than those of Eppinger and Charnas

Methods based on fluorescence alone, whether colorimetric or dilution, are subject to two criticisms in general regardless of the individual procedures The fluorescence with zinc salts varies considerably with conditions present in the solution, and while these may be adjusted according to Marcussen and Hanson, no method employing fluorescence has been based on a crystalline substance, with the exception of that recently described by Opitz and Choremis in which Fischer's mesobilirubinogen was used to standardize a modification of Adler's earlier technic Adler has pointed out the extreme range of strength of fluorescence of the urobilins of various writers, hemibilirubin or mesobilirubinogen, after oxidation, having a much more intense fluorescence than any of the other materials In addition to this, the lack of chemical

individuality of urobilin, together with Fischer's belief that what is commonly designated as urobilin in the urine is probably urobilinogen in some relation with a fluorescent derivative of a bile acid or cholesterol, casts doubt on the usefulness of fluorescence and will continue to do so until (according to Fischer) there are reported more exact quantitative analyses of urobilin-containing urines as to urobilinogen, bile acids and cholesterol. Adley has recently abandoned his method based on fluorescence in favor of a new extraction apparatus for quantitation of mesobilirubinogen. The method used by Elman and McMaster in their experimental work was a colorimetric procedure in which fluorescence was compared with standard acriflavine solution, the latter originally standardized with urobilin isolated by a modification of Garrod and Hopkins' technic. This method of quantitation has recently been employed by Royer in a variety of clinical investigations and by Edelman, Halpern and Killian in demonstrating the prognostic value of urobilinuria in cardiac failure.

Methods depending on dilution of absorption bands have been considerably used, more particularly in the United States, where the technic described by Wilbur and Addis, in 1914, has been popular. These investigators did not believe it possible to standardize any method on a chemical individual (although their publication was subsequent to that of Fischer's work on urobilinogen). In this method, the absorption bands of the zinc compound of urobilin and the urobilinogen-aldehyde dye are diluted out one at a time in the same solution of urine or stool, the sum of the two dilutions is the value reported. Dilution values for either absorption bands or fluorescence are subject to the personal equation in marked degree. Another objection to this method has recently been pointed out by Terwen, *i. e.*, that since indol and skatol produce the same color and absorption band as does the urobilinogen-aldehyde compound (550-570), it is obviously necessary to remove these substances and this was not taken into account by Wilbur and Addis. Sallet and Simpson had previously used spectroscopic dilution procedures based on the urobilin band alone.

Charnas, as mentioned previously was the first to apply the aldehyde reaction to a quantitative method. Some loss of urobilin undoubtedly occurred by this method as well as by that of Brugsch and Retzlaff, in the attempt to remove the interfering indol-skatol. The dilution methods of Flatow and Brunell and of Wallace and Diamond neglect these substances. With the doubtful exception of Charnas' fermentation transformation of urobilin to urobilinogen, all of these methods attempted to measure only the preformed urobilinogen. In 1925, an admirable method was described by Terwen in which urobilinogen, both preformed and oxidized, is estimated as one, and indol-skatol definitely eliminated. Here again the question of chemical identity of urobilin

arises it is definite that urobilinogen develops increasing fluorescence on exposure to air and light and becomes darker while the urobilin absorption band appears in such an exposed solution. Terwen was able to show that the Ehrlich reaction increased, and that the urobilin band diminishes or disappears with reduction of the type used in his method. In 1927, an apparatus for the quantitative extraction of mesobilirubinogen was reported by Adler, and a year later (1928) clinical results with this method were published by Adler and Biessel. Terwen's method was standardized on a noncrystalline urobilin, while Adler's procedure estimates only the preformed urobilinogen.

DESCRIPTION OF METHOD

Of the foregoing methods, that described by Terwen was believed superior for clinical application. While Adler's technic quantitates a chemical individual, the apparatus is too complicated for the average clinical laboratory, and although the method is said to be colorimetric, no details of the colorimetric procedure are given. Terwen's method was applied to both urine and feces, reduction and alkaline extraction are carried out simultaneously by a ferrous hydroxide precipitate with an excess of sodium hydroxide. The clear filtrate should not contain any urobilin band, it is acidified with strong tartaric acid and the urobilinogen extracted with ether. Paradimethylaminobenzaldehyde in ether is added to a portion of this in another separatory funnel followed by concentrated hydrochloric acid, a little distilled water and a small amount of a saturated solution of sodium acetate. The latter is important, since Terwen was able to show that the red color formed by indol and the aldehyde is stable only in the presence of a mineral acid, while the urobilinogen-aldehyde color is unaffected by the formation of acetic acid. The acetic acid is also less likely to promote oxidation of the urobilinogen. Precipitation of any excess aldehyde in the lower aqueous fraction is effected, so that the yellow color returns to the ether. All of these changes are undoubtedly attributable simply to a decrease in the hydrogen ion concentration of the aqueous portion. More than one extraction is necessary if considerable urobilinogen is present. The final colored solution is compared in an Autenrieth colorimeter with a standard sodium carbonate-phenolphthalein solution. This method was modified in the following ways, and was standardized with crystalline hemibilirubin or mesobilirubinogen (urobilinogen), as discussed later.

- 1 A greater dilution was used in the primary extraction. Ferrous sulphate was used rather than ferrous ammonium sulphate as in Terwen's method, with relatively more of the ferrous salt and relatively less sodium hydroxide. This makes both the extraction and reduction more efficient.

- 2 The period of reduction was shortened to one hour. Terwen indicated that reduction was complete within a relatively short time, but stipulated that the original flask should be set aside over night. In my experience, the filtrate usually presents no urobilin absorption band after one hour, while one is not infrequently present when left over night. Furthermore, repeated colorimetric comparisons at intervals indicated that the optimum reduction is reached within from forty-five to ninety minutes.

- 3 Suction flasks were used for the primary extraction and reduction with evacuation to hinder reoxidation.

4 Occasional supplementary reduction in the filtrate was obtained with small amounts of sodium amalgam. The presence of a definite urobilin band in the filtrate requires further reduction, and this is more easily accomplished by adding a small amount of 5 per cent sodium amalgam to 10 or 15 cc. of filtrate for a short period than to recommence with larger amounts of the ferrous salt and sodium hydroxide. Adler suggested that reduction, as in Terwen's method, might produce some undesirable effect on the urobilinogen. Terwen's control experiments did not indicate the existence of any such effect, and I did not find any significant variation in color before and after sodium amalgam had been in contact for a short time with a filtrate in which ferrous hydroxide reduction had just previously taken place.

5 The amount of filtrate used was varied to correspond to the relative amount of urobilinogen present, thus making the method more sensitive and the color comparisons more uniform, as well as reducing the number of extractions to a minimum. Terwen used a fixed amount of filtrate, 2 cc. in analyses of the stools and 20 cc. in the case of urine. Furth and Singer recently pointed out the advantage of using large amounts of filtrate in estimating minute quantities of urobilinogen in the stool, as when an incomplete obstructive jaundice exists.

6 The method of using the entire ether extract was simplified so that only one separatory funnel is necessary, without any transference of solutions. Terwen's use of an aliquot of the ether extract is assumed to be due to the slight solubility of ether in water or to retain in reserve some of the ether extract in case a check was believed necessary, however, even when the original filtrate is rich in urobilinogen, after one ether extraction the aqueous fraction fails to give any aldehyde reaction. If a check is considered advisable, it is more satisfactory to begin with fresh unexposed filtrate. Emulsions are uncommon and do not give rise to difficulty.

7 Acetic rather than tartaric acid was used for acidification of the alkaline filtrate. This is more convenient and does not produce any error. Comparative estimations on the same filtrate failed to show any loss when acetic acid was employed. This was also the experience of Furth and Singer. Terwen presumably used tartaric acid because of its insolubility in ether. In the present method, the urobilinogen remains in the ether for only a short period, in any event, some acetic acid is present in the end-solution.

With these modifications, the method of analyses of the feces and urine is subsequently given. The manner in which stools are collected, weighed and mixed prior to the estimation is described in detail. It is believed of greatest importance to obtain the average value for several days. This is also the opinion of Adler and of Opitz and Choremis. It is obvious that with many persons estimation of the fecal urobilinogen for twenty-four hours is of little value because of the considerable variation in the amounts of stool. Wilbur and Addis observed marked fluctuations of urobilin in the urine from day to day. The following method estimates preformed urobilinogen and urobilinogen which has been changed to the substance ordinarily known as "urobilin."

Collection of Feces—If the patient is having regular defecation of formed stools daily at relatively the same time, it is sufficient to save all stools for four days, counting from an hour at which one was discarded. The last stool is collected at relatively the same hour four days later. Specimens for the first and second forty-eight hours are collected separately and analyzed separately at the end of two and four day intervals. In this way the output of urobilinogen may be followed over some period by the daily average for consecutive two day periods, or the daily average for a single four day period may suffice. Specimens are

most conveniently kept in the ordinary cylindric waxed cardboard cartons of liter capacity. These will usually contain all of the forty-eight hour stool unless enemas have been necessary. They should be kept in a cool place, with exclusion of light, during the period prior to analysis.

Satisfactory collection for analysis is much more difficult in persons who are not having regular defecation. In spastic constipation, it is advisable to defer the period of collection for a few days until antispasmodics and nonirritating roughage have brought about normal bowel movements. In atonic conditions, cascara in moderate doses is believed advisable. Mineral oil by mouth or oil enemas are not advisable. Whenever the patient to be studied does not have regular stools at approximately the same time daily, it is best to begin the period of collection with a water enema (from $\frac{1}{2}$ to 1 pint) the results of which are discarded, exactly four days later, another enema is given the results of which are included with the last forty-eight hour collection. If the amount of stool during the four day period is very small and fecal impaction is found on rectal examination, this should be broken up with the gloved finger and a water enema of 1 pint administered, the results of which are included in the collection. It is often difficult to study the excretion of urobilin in the stool in persons who are critically ill, both because they do not eat a sufficient amount to create residue and because of the atonic condition of the bowels. A certain amount of residue is undoubtedly necessary to promote excretion at a normal rate, since, as Wilbur and Addis have observed, the output of urobilinogen is diminished in constipation, presumably because of the greater time allowed for resorption. It is probable that values will be too low unless the total amount of stool examined for the four day period is at least from 250 to 300 Gm, depending on the size of the person. This is, of course, exclusive of enema fluid. The collection of stools during a period of diarrhea is not advisable since the rapid passage of intestinal contents fails to permit normal resorption. In reporting estimations of the daily output of urobilin, it is advisable to mention the amount of the four day stool specimen.

Measurement and Mixture of Stool Specimens—The entire forty-eight hour specimen must be weighed prior to analysis. An empty container of the same size as that containing the specimen is placed on the balance pan opposite the specimen. In this way the stool may be weighed directly. The forty-eight hour stool specimen must be mixed so that all parts are relatively equal. In the case of stools having at least a moderate degree of consistency, mixture may be made in the collection container directly. The iron rod of a ring stand is useful for this purpose, as it is easily cleaned. Stools that are liquid or partly so must be thoroughly homogenized in a large mortar. If the specimen is partly solid and partly liquid, mixture is best accomplished by first pouring the liquid portion into a beaker, transferring the solid portion to the mortar where it is ground up with the pestle, and then adding the liquid from time to time until all is thoroughly mixed.

Method of Quantitation—The following materials are required: 1 liter mortar and pestle, one small mortar and pestle, one 250 cc evaporating dish, one suction flask of 250 cc capacity equipped with a 12 inch length of heavy walled rubber tubing fitted on the suction arm, a few plain stiff clamps or hemostatic forceps (strong pinchcocks may be used), several 5 cc pipets graduated in 1 cc, and 1 cc pipets graduated in 0.1 cc, a spectroscope (small hand size is sufficient), a Van Slyke type of separatory funnel capable of holding 250 cc, a few ordinary 15 to 20 cc test tubes and a few 50 or 100 cc graduated test tubes or cylinders, and a colorimeter, preferably of the DuBoscq type although any reasonably accurate colorimeter may be used. In the present series of estimations, a Klett biocolori-

meter was employed. If more than one determination is to be made, it will be necessary to have two or three of the suction flasks.

The following reagents are required. Ehrlich's reagent, composed of 10 Gm of paradimethylaminobenzaldehyde, 75 cc of concentrated hydrochloric acid and 75 cc of distilled water, crystalline ferrous sulphate ($\text{FeSO}_4 \cdot 12 \text{H}_2\text{O}$), 10 per cent sodium hydroxide, 5 per cent sodium amalgam, 20 per cent acetic acid, pure ether (diethyl), saturated ethereal solution of para dimethylaminobenzaldehyde (should be light yellow, as definite redness or darkness indicates impurity), concentrated hydrochloric acid in a dropping bottle, a saturated solution of sodium acetate (aqueous), a saturated solution of sodium carbonate (aqueous), 0.05 per cent alcoholic solution of phenolphthalein (50 mg of pure phenolphthalein in 100 cc of 95 per cent alcohol kept in a glass stoppered bottle will suffice for a large number of determinations).

Procedure for Analysis—Weigh out 5 Gm of the mixed stool on filter paper, or if not sufficiently dry, in an evaporating dish. Transfer to a small mortar. The ordinary cheap wooden tongue depressor is very useful in weighing and transferring. Add a small amount of water from a measured portion of 95 cc. Grind thoroughly with a pestle, it is important that the particles of feces be finely ground. Adler has observed that small fecal particles adsorb urobilin and hinder extraction. Add the remainder of the water and again mix completely. Let this mixture stand a moment or two while measuring out 50 cc of 10 per cent sodium hydroxide. Decant the supernatant portion from the mortar into a small flask (Florence, preferably). Again grind up the remaining precipitate and fluid, then add the 50 cc of sodium hydroxide and add all of this to the first portion in the flask. Shake vigorously for a few moments. Pulverize 10 Gm of ferrous sulphate on the filter paper on which it was weighed and place in the 250 cc suction flask, the side arm of which is fitted with heavy walled rubber tubing. Add 46 cc of distilled water and shake until the majority has gone into solution. Now add to this in small portions and with vigorous shaking all of the fecal emulsion from the other flask. Cork tightly and evacuate with suction. When vacuum is considerable, clamp the rubber tube with forcep or stiff clamp. Set aside in the dark for one hour. At the end of this period, filter from 3 to 4 cc into an ordinary test tube. Examine this with a hand spectroscope for the presence of a definite absorption band of alkaline urobilin (495-515). Rarely more than a faint urobilin band is seen, and in this event further reduction is necessary. To approximately 15 cc of the filtrate in a 50 cc graduated centrifuge tube, add from 1 to 2 Gm of 5 per cent sodium amalgam. Cork lightly and set aside in the dark for ten minutes. A second period of ten minutes may be necessary for disappearance of the urobilin band. If sodium amalgam is not at hand, the following method may be substituted: weigh out another 5 Gm of the mixed stool specimen and proceed exactly as before, except use double the amount of both the 20 per cent ferrous sulphate and the 10 per cent sodium hydroxide (100 cc), this makes the value of the primary dilution 60, while it is ordinarily 40.

To a few cubic centimeters of the urobilin-free filtrate (as examined spectroscopically) in a test tube, add Ehrlich's reagent from a dropping bottle, drop by drop, until cloudiness has disappeared. The amount of red which develops immediately determines roughly how much filtrate is to be used in the quantitative determination. The following is a useful, but not necessarily absolute, list of the degrees of color and corresponding amounts of filtrate to be used: (1) deep red with a slight bluish tinge, 1 cc, (2) light red, 2 cc, (3) pink, 5 cc, (4) barely discernible pink, 10 cc, (5) no color and absent urobilinogen—aldehyde absorption band—(550-570), from 25 to 50 cc. (If a new specimen, 50 cc should be

employed, but if color has recently been present in previous specimens, 25 cc is probably enough)

In a series of determinations made every other day on specimens from the same patient, after the first day it is usually sufficient to use the same amount of filtrate each time

Place the amount of filtrate chosen in a separator funnel and acidify with an excess of 20 per cent acetic acid (0.4 cc per cubic centimeter of filtrate constitutes a definite excess) At once add approximately 40 cc of pure ether (diethyl) The amount need not be exactly measured Shake vigorously for from two to three minutes (When larger amounts of filtrates are used, the shaking must be relatively more gentle, from 75 to 100 inversions will suffice) Allow the aqueous fraction to separate, then drain it off and discard Wash the ether once with a small portion of distilled water, and discard the latter From a 5 cc pipet add 3 cc of a saturated ethereal solution of paradimethylaminobenzaldehyde Add 10 drops of concentrated hydrochloric acid from a dropping bottle Shake vigorously for from one to two minutes Add a few cubic centimeters of distilled water and shake briefly Add 3 cc of a saturated aqueous solution of sodium acetate and again shake Separate off the colored solution into a 50 cc graduated centrifuge tube or cylinder Place this in a glass or rack and cover temporarily with a cloth or towel Repeat the following extraction, using only 5 drops of hydrochloric acid, a smaller amount of water and 2 cc of the sodium acetate solution More of the aldehyde need not be added If not too much filtrate is chosen in the first instance, three such extractions will suffice Sometimes, when the amount of urobilinogen is large, four or five extractions will be necessary The last extraction should yield only a faint color When all of the colored aqueous portions have been collected in the same graduated tube, this collection is made up to a volume which is a multiple of the original amount of filtrate taken If the color is pale, dilution should be only to the next cubic centimeter This solution is thoroughly mixed, and a portion of it is placed in one colorimeter cup Some of the standard phenolphthalein solution is placed in the other cup This is composed as follows (according to Terwen) 1 cc of 0.05 per cent alcoholic solution of phenolphthalein, and 5 cc of saturated aqueous solution of sodium carbonate Make up to volume with distilled water in 100 cc volumetric flask Prepare fresh the same day

As subsequently shown in detail, this standard solution has a color equivalent so that of 0.4 mg of urobilinogen condensed with paradimethylaminobenzaldehyde and hydrochloric acid in 100 cc Calculations are then as follows D_1 (usually 40) $\times D_2 = \frac{\text{Volume of final solution}}{\text{Volume of filtrate used}} \times \frac{S}{R} \times 0.4 = \text{mg of urobilinogen in 100 Gm of stool}$ Multiply this by the weight of the entire stool specimen and divide by 100 to obtain the total amount of urobilinogen At the end of the period of collection (usually four days), the amounts obtained are added together and the sum divided by the number of days This final result is the average daily output in milligrams

The foregoing extraction procedure should be carried out in subdued light, preferably artificial

It is essential that no alkali should come in contact with the final colored solution as the dyestuff is decomposed by alkali, with complete loss of the red color (Fischer)

Collection of Urine—Urine is collected for two forty-eight hour periods in gallon bottles in which have been placed from 20 to 30 cc of a saturated alcoholic solution of salicylic acid, for preservation (The salicylic acid has been shown

by Terwen not to have any effect on the subsequent estimation) During collection, these bottles should be kept in a cool, dark place

The forty-eight hour urine should be mixed and measured. If deeply colored, or if bilirubinuria is suspected, bilirubin should be tested for, the Gmelin, Huppert-Cole or van den Bergh test being used. If bilirubin is found to be present in more than traces, preliminary treatment is necessary to eliminate it, as with the foregoing method a certain amount of color may be produced by the reduction of bilirubin alone, in the absence of urobilinogen. (Pure bilirubin was dissolved in 10 per cent sodium hydroxide, this was added to 20 per cent ferrous sulphate as in the foregoing procedure, and after standing in the dark one hour the filtrate was found to give a definite aldehyde reaction with the same extraction technic used for the stool filtrate. Terwen apparently did not consider that the bilirubin was reduced in any degree, as he advises the use of petroleum ether in place of ether which, he states, does not extract bilirubin from the acidified filtrate.)

To free the urine of bilirubin, add to 200 cc of urine 100 cc of a saturated aqueous solution of calcium hydroxide with slight excess not in solution, and to which has been added a relatively small amount of 10 per cent sodium hydroxide. Shake these solutions together in a beaker and let stand for a short time. The bilirubin is precipitated as insoluble calcium bilirubinate. Then filter. The filtrate is used in place of bilirubin-free urine in other determinations and the added dilution of 1.5 is taken into account in the final calculation.

To 5 Gm of ferrous sulphate in the suction flask with rubber tubing on the suction arm, add 23 cc of distilled water. To this add 100 cc of the mixed bilirubin-free urine, or filtrate to be tested. Then add in small portions at a time and with constant shaking 25 cc 10 per cent sodium hydroxide. Evacuate, clamp and set aside in dark for one hour. The procedure from now on is the same as in the case of the determination on the stool, except that it is necessary to use larger amounts of filtrate, especially with normal urines and bilirubin filtrates of urines containing small amounts of urobilin. Fifty cubic centimeters of filtrate should be employed in such instances.

Normally, there is rarely more than a trace of urobilin present in the urine, and the amount of color obtained from 50 cc of filtrate is often so small that accurate comparison of the color is impossible. It is better in such an instance to report simply a trace, rather than a figure which is not liable to be accurate. In the present series more than 50 cc of filtrate have not been used.

When urine alone is used, the method of calculation is as follows:

$$D_1 (1.5) \times D_2 \left(\frac{\text{Final volume}}{\text{Amount of filtrate}} \right) \times \frac{S}{R} \times 0.4$$

This multiplied by the number of cubic centimeters of urine in the entire specimen and divided by 100 gives the total number of milligrams present.

When calcium hydroxide has been used to precipitate bilirubin, the calculation is done as follows:

$$D_1 (1.5) \times D (1.5) \times D_2 \left(\frac{\text{Final volume}}{\text{Amount of filtrate}} \right) \times \frac{S}{R} \times 0.4$$

STANDARDIZATION OF METHOD AND DATA RELATIVE TO THE OTHER MODIFICATIONS

1. Strength of the standard phenolphthalein solution in terms of milligrams urobilinogen per hundred cubic centimeters. Since no figure was found in the literature representing the equivalent of a definite amount of crystalline urobilin-

ogen condensed with Ehrlich's reagent, with a standard color solution, the following experiments were undertaken .

(a) Hemibilirubin or mesobilirubinogen was prepared in small quantity according to the procedure described by Fischer, with decrease in all amounts corresponding to decrease in bilirubin (The latter is very expensive whether purchased pure or obtained from gallstones of cattle) Bilirubin (Eastman), 200 mg was dissolved in 3 cc of tenth-normal sodium hydroxide, to which was added 1.5 cc of water. This was reduced over night in a 10 cc Erlenmeyer flask with approximately 5 Gm of 46 per cent sodium amalgam. The light brown solution was acidified with 50 per cent sulphuric acid and shaken out four times with 4 cc



Mesobilirubinogen crystals

amounts of chloroform. The latter was dried superficially over anhydrous sodium sulphate, after being filtered. It was then concentrated in partial vacuum in an atmosphere of carbon dioxide and protected from the light. The remaining syrup was taken up in about 4 cc of ethyl acetate, 3 cc of petroleum ether added, filtered and again concentrated in the same way, then again taken up in hot acetic ester (from 4 to 5 cc), to which a little petroleum ether was added, filtered and cooled. A small separation of apparently colorless, very small crystals took place. These were filtered off and the mother liquor concentrated to a small volume, so that the yield was increased to approximately 20 mg. It was placed at once in a vacuum desiccator over P_2O_5 . A few of the crystals were examined

and found to be apparently identical with those of hemibilirubin described by Fischer. No measurements were made. The hemibilirubin crystals as observed are shown in the sketch. While the substance was apparently colorless on first crystallization, it quickly assumed a light reddish yellow or orange tint.

With this pure substance, the following determinations were made (all weighings were made with a microbalance sensitive to 0.000001 Gm.)

(1) The substance, 0.0009625 Gm. was mixed with approximately 20 cc. of ether, 3 cc. of saturated ethereal solution of paradimethylaminobenzaldehyde was added, then 10 drops of concentrated hydrochloric acid. This was shaken two minutes. A little water was added, shaken briefly, then 4 cc. of saturated aqueous solution of sodium acetate was added, and the substance again shaken. The colored aqueous solution was drawn off. Shake-outs were repeated in the same way, from 5 to 8 drops of hydrochloric acid and 3 cc. of sodium acetate solution being used until no more color could be extracted. The final volume was 102 cc. This was compared in the colorimeter (Klett) with the standard phenolphthalein solution previously described. Standard 20, $R = 8, 8.5, 7.9, 8.2$, average, 8.15. Since 0.943 mg. was present in 100 cc. $\left(\frac{100}{102} \times 0.962\right)$, $\frac{8.15}{20} \times 0.943 = 0.384 =$ mg. per hundred cubic centimeters equivalent to the standard phenolphthalein solution.

On three more occasions, shortly after this, with the same procedure and varying amounts of mesobilirubinogen, the following figures were obtained:

0.0006497 Gm. to 100 cc. S20 $R = 11.5, 10.3, 12.4, 11.5$ av. 11.4, 0.370 mg. per 100 cc.

0.001980 Gm. to 250 cc. S20 $R = 9.5, 8.9, 10.0, 9.4$ av. 9.4, 0.371 mg. per 100 cc.

0.001935 Gm. to 250 cc. S20 $R = 9.6, 10.2, 10.4, 10.5$ av. 10.2, 0.394 mg. per 100 cc.

The average of these four determinations was 0.379 mg. per hundred cubic centimeters \approx to the phenolphthalein standard. (S indicates standard, R, urobilinogen solution.)

(2) Three more determinations were obtained in the same way, except that the crystalline substance was dissolved in 20 cc. of 10 per cent sodium hydroxide, which, with 20 cc. of water was added, with shaking, to 20 cc. of 20 per cent ferrous sulphate in a small Erlenmeyer flask. This was evacuated and left in the dark for one hour. At the end of this period, 5 or 6 cc. of the filtrate, varying in different instances, was acidified with 20 per cent acetic acid and shaken out with a large volume of ether (from 20 to 30 cc.). The procedure, thenceforth, was the same as that already described. The values obtained were 0.429, 0.430, 0.429 mg. per hundred cubic centimeters \approx to phenolphthalein standard. It seemed evident that a moderate, though constant, loss occurred in these instances. Deterioration of the substance was not believed to be responsible since the first determination was carried out within an hour of the last of those already mentioned. The primary extraction with ether was complete, and all of the color was extracted from the ether so that only the ferrous hydroxide precipitate was left in question. According to Terwen, the ferrous hydroxide does not adsorb any urobilinogen and it is true that extraction of alcohol of this precipitate has failed to show color with Ehrlich's reagent. Adler stated that the intensity of red in alcoholic solution increases to a maximum only after from twenty to twenty-five minutes, and that in alcoholic solution certain proportions of alcohol and water are optimal. Since the color is entirely removed in the present method by repeated condensations into a final aqueous solution, these conditions are not parallel, so that no interference is believed to have arisen in this way. A fourth determination was made in which 20 cc. of urobilin-free urine was substituted for the water as in the foregoing instance. Here 0.004264 Gm. of mesobilirubinogen were dissolved in 60 cc., reduced one hour, then 5 cc. of filtrate acidified, extracted and

finally diluted to 250 cc $S = 10$, $R = 287, 284, 286, 285$, average 285 Five cubic centimeters of filtrate contained 0.3553 mg diluted to 250 cc

≈ 0.142 mg in 100 cc $\times \frac{285}{100} = 404$ mg /100 cc \approx phenolphthalein standard

(b) Since Fischer considered the molecular weights of bilirubin and hemibilirubin to be relatively the same, it was believed that a constant equivalent color value from varying amounts of pure bilirubin reduced in different experiments, would be of considerable assistance in standardizing the phenolphthalein solution With this in mind, the following determinations were carried out (this investigation was made prior to that previously described) 0.0598 Gm of pure bilirubin (Eastman) dissolved in 50 cc of tenth-normal sodium hydroxide and 10 Gm of 5 per cent sodium amalgam were added (The balance used for this weighing was sensitive only to 0.1 mg) One hour later, 10 Gm more of sodium amalgam was added Then at the intervals subsequently given small measured portions (from 0.2 to 0.5 cc) of the filtrate were removed, acidified with 20 per cent acetic and all of the aldehyde reacting substance shaken out as in the routine procedure and compared with the phenolphthalein standard The equivalent values in milligrams per hundred cubic centimeters at the different periods are given under (a) Under (b) and (c) are given the results of two similar sets of determinations, with the primary amount of bilirubin used in each instance

(a)	(b)	(c)
0.0598 Gm bilirubin reduced	0.0302 Gm	0.04265 Gm
2 hrs 0.797	1 hr 1.2	1 hr 0.742
3 hrs 0.542	2 hrs 0.906	2¼ hrs 0.75
4 hrs 0.422	3 hrs 0.906	3½ hrs 0.68
6½ hrs 0.478	4 hrs 0.98	4½ hrs 0.88
8 hrs 0.458	6½ hrs 1.2	
21 hrs 0.717		
24 hrs 0.917		
72 hrs 1.315		

From this it was evident that no constant value might be obtained, although it was considered significant that the lowest value obtained, 0.422, was obtained with the largest sample of bilirubin, and hence was liable to the smallest error, particularly as regards the influence of oxidation, this value was of the same magnitude as those obtained in the determinations with mesobilirubinogen

(c) "Urobilin" was isolated from feces according to the procedure described by Terwen This was reduced in varying small amounts on three occasions with ferrous hydroxide The values in milligrams per hundred cubic centimeters \approx to the standard were 0.44, 0.40 and 0.39 In these determinations the filtrate was analyzed at one-half hour intervals for several hours and the maximum amount of color found used in calculation The optimum period varied from forty-five to ninety minutes

After consideration of all of the foregoing observations it is believed that the value 0.4 first given by Terwen, is satisfactory for clinical usage On the basis of theory it was first believed that 0.3 should be the correct figure since the ratio of the molecular weights of hemibilirubin and of Terwen's urobilin are 3:4 That the values are however practically the same may be explained either on the basis

of a dipyrrol impurity in Terwen's material or an error in the molecular weight determination of 758 (micromethod, boiling point of camphor)

2 Determinations with the clinical quantitative method previously described under varying conditions

(a) Urine

Primary dilution 15 second dilution 5 $S = 10$, $R = 10$

$$15 \times 5 \times \frac{10}{10} \times 0.4 = 3 \text{ mg per 100 cc}$$

Same, except with primary dilution with calcium hydroxide solution, as for precipitation of bilirubin

$$15 \times 15 \times 4 \times \frac{10}{12} \times 0.4 = 3 \text{ mg per 100 cc}$$

(b) With different amounts of filtrate

5 cc

$$15 \times 3 \times \frac{10}{10} \times 0.4 = 1.8 \text{ mg per 100 cc}$$

50 cc

$$15 \times 1 \times \frac{20}{67} \times 0.3 = 1.76 \text{ mg per 100 cc}$$

(c) After standing with salicylic acid preservative (Terwen was able to show that salicylic acid alone did not have any influence on the values obtained)

The urine contained 1.76 mg in 100 cc

Five days later, it contained 1.45 mg in 100 cc

(d) Duplicate determinations on the same stool specimens with different weighings and extractions

(1) 53.3 mg per 100 Gm

60 mg per 100 Gm

(2) 195.5 mg per 100 Gm

209 mg per 100 Gm

(3) 269.5 mg per 100 Gm No urobilin band in filtrate

221.5 mg per 100 Gm Definite medium faint alkaline urobilin band in filtrate (500-510)

(e) Supplementary reduction with sodium amalgam

Sample of feces Primary dilution 60 final dilution 16, $S = 10$, $R = 18$

$$60 \times 16 \times \frac{10}{18} \times 0.4 = 213.2 \text{ mg per 100 Gm}$$

Same filtrate allowed to stand in sunlight until a definite urobilin band appeared, then 10 cc reduced with 1 Gm of 5 per cent sodium amalgam, five minutes (at the end of this period, colorless and without urobilin band)

$$60 \times 13 \times \frac{10}{15} \times 0.4 = 208 \text{ mg per 100 Gm}$$

A second stool filtrate with a medium heavy urobilin band

$$40 \times 13 \times \frac{10}{12} \times 0.4 = 173.3 \text{ mg per 100 Gm}$$

One gram of 5 per cent sodium amalgam added to about 10 cc of the same filtrate After twenty minutes urobilin band is hardly discernible

$$40 \times 14 \times \frac{10}{11} \times 0.4 = 201.8 \text{ mg per 100 Gm}$$

3 Efficiency of ether extraction for large amounts of filtrate (Terwen was able to show that with small amounts of filtrate one ether extraction sufficed to remove 96 per cent of the urobilinogen)

On two occasions 50 cc of filtrate from urines rich in urobilin were acidified and extracted, once with ether in the ordinary way. The aqueous fractions were then acidified with sulphuric acid and saturated with solid ammonium sulphate. They were then extracted with from 10 to 15 cc of amyl alcohol. Only a very faint urobilin band was demonstrable in either of these extracts, which, considering their concentration indicates satisfactory extraction with one shake-out.

4 Quantitative range of method. By concentration of large amounts of filtrate, the method becomes very sensitive. Thus, 1,970 cc of urine was found to contain 1.044 mg, when 50 cc of filtrate was concentrated to 6 cc, or 0.053 mg per hundred cubic centimeters. On another occasion 1,760 cc of urine contained 1.026 mg or 0.05 mg per hundred cubic centimeters, after 50 cc of filtrate was diluted to 10. The color in this instance was slightly too yellowish for accurate comparison. In general, the method is believed to be sensitive to between 0.05 and 0.1 mg per hundred cubic centimeters, the variation depending on the concentration employed.

CLINICAL OBSERVATIONS

In the following pages are summarized the observations in a series of normal and abnormal persons on whom the foregoing method was employed. Stools were collected as a routine measure for four days. Single investigations of urine were usually made for the same period, if consecutive forty-eight hour specimens were utilized. In any case, the reported value is an average twenty-four hour amount. Hemoglobin estimations were made with a Klett colorimeter and Newcomer disk which was checked gasometrically. Reticulocyte counts were done by the smear method. Van den Bergh's original qualitative technic was used. The quantitative procedure was not employed. Bernheim's icterus index method was used with a standard disk for a Klett colorimeter (supplied by Klett and Company). The range of normal with this apparatus was from 5 to 8. Even when serum is obtained with the greatest care small amounts of hemoglobin are usually discernible with the spectroscope and this is undoubtedly responsible for a small undetermined error. Bilirubin in urine was recognized by the Gmelin reaction carried out on filter paper.

In employing the foregoing values, 175 mg per day for feces was considered the upper limit of normal for females and 250 mg per day for males. It is probable that greater uniformity would be attained with a larger and more representative normal series. The females were nurses on hospital duty, several of whom had slightly subnormal hemoglobin percentages and erythrocyte counts. The males were ambulatory patients in the hospital for relatively minor conditions, believed irrelevant although it is not impossible that previous tonsillectomy in one instance may have increased the value. No definite relationship was noted between body weight and elimination of urobilinogen.

The results in the cases of pernicious anemia will be discussed collectively later. In the following paragraphs clinical results are corre-

Urobilinogen Elimination and Other Laboratory Observations

Diagnosis	Sex	Age	Weight	Date	Hemo globin	Red Blood Cells	Reticulo- cytes, Van per Cent	Van Bergh	Urine, Icterus Index	Urine, Uro- bilin	Uro- bilin	Stool, Uro- bilin
Normal (1)	M	25	165	5/ 4	14.2	4.44				0	0.7	192.3
Normal (2)	M	23	163	2/ 4	15.8	4.78	(1 week postton- silectomy)			0	0.9	245.7
Normal (3)	M	61	150	2/25	13.5	4.22				0	Trace	217.4
Normal (4)	M	27	192	1/ 6 2/ 4	16.8 (10 days posttonsilectomy)	4.77				0	Trace	174.9
Normal (5)	M	28	170	5/14						0	0.5	117.4
Average daily elimination for males												189.5
Normal (6)	F	20	113	5/ 4	13.9	4.9				0	Trace	54.4
Normal (7)	F	20	155	4/28	12.9	4.14				0	Trace	162.4
Normal (8)	F	20	107	3/30	14.6	4.38				0	0.25	134.0
Normal (9)	F	19	174	4/ 1	14.8	4.40				0	Trace	149.6
Normal (10)	F	22	134	4/ 7	15.0	4.61				0	Trace	107.7
Normal (11)	F	20	123	4/15	13.1	3.96				0	0.4	89.6
Normal (12)	F	21	164	4/19	13.9	4.10				0	Trace	122.3
Normal (13)	F	20	127	4/24	13.5	4.09				0	Trace	83.4
Average daily elimination for females												112.9
Average daily elimination for both sexes												151.2
Secondary anemia (1)	F	17	102	12/13 12/29	11.8	3.58			7.5	0	Trace	66.2
Secondary anemia (2)	F	53	117	12/ 3	7.0	2.9	0.4		5.0	0	0.9	18.3
Secondary anemia (3)	F	29	112	12/30	9.5	2.73	0.2		8.0	0	0.8	35.5
Secondary anemia (4)	F	19	106	5/ 8	12.3	3.72					0.0	51.7
Pernicious anemia (1)	M	63	144	1929 4/30 11/27 11/30 12/ 2 12/ 4 12/ 7	12.2 11.8	3.71 2.49	0.4 0.4 3.2			0	6.87 (Six day col- lection)	127.0
								Delayed 9.5				
Pernicious anemia (2)	F	59	150	3/ 3	4.4	0.87	0.8		27.0	0	3.4 (48 hour col- lection)	1179.5
Pernicious anemia (3)	M	54	170	1/22 1/24 1/27 1/29 2/ 1 2/ 4 2/ 7 2/13 2/14 3/10 3/12	5.8 6.0 6.0 7.9 8.5 11.6 12.5 16.1	1.12 1.33 1.78 2.56 2.56 3.81 4.84	0.9 0.8 1.6 1.6 18.6 9.0 5.0 0.1 0.0		10.7 0	1.2 Trace Trace	902.8 299.0 172.9	
Pernicious anemia (4)	F	63	141	3/11 3/15 3/17 3/21 3/27 4/ 3 4/ 9	10.9 10.4 11.2 11.2 12.3 12.2	1.92 1.93 2.4 2.66 2.88 3.07	0.36 5.2 4.1 3.4 1.3		5.4	0	2.2 1.5 Trace 70.4	260.9
Pernicious anemia (5)	F	56	93	3/ 6 3/11 3/13 3/15 3/20 3/22 3/26 4/ 2 4/ 4 4/ 8 4/10	3.9 4.1 8.0 8.5 9.0	1.03 1.49 2.4 3.16 3.65	2.6 4.4 19.0 1.9 0.95 1.0		17.0	0	1.8 27.2 8.1 1.5 Trace 0.0 0.0 0.85	279.0 357.7 177.4

Urobilinogen Elimination and Other Laboratory Observations—Continued

Diagnosis	Sex	Age	Weight	Date	Hemo- globin	Red Blood Cells	Reticulo- cytes, per Cent	Van den Bergh	Urine, Icterus Index	Urine, Bilin rubin	Uro- bilin	Stool, Uro- bilin
Permeious anemia (6)	M	74	170	1/11	62	132						
				1/13			0.4	Delayed	12.5			
				1/14			0.6			0	18.5	
				1/16			0.3					249.1
				1/17			0.2					
				1/18	70	141						
				1/21	72	166	10.6				2.7	
				1/23							0.6	484.7
				1/24	77	189	9.8					
				1/29	80	214	9.6					
				1/31	80	257						
				2/4			1.0					
				2/6	83	229						
				2/14	118	29	0.5					
				2/20	127	307						
				2/27	133	315						
				3/6	140	333						
				3/13	144	407						
				5/13							0.68	216.5
Permeious anemia (7)	F	62	158	1/6	40	083	1.0	Delayed	15.0			
				1/8			1.2			0	81.5	
				1/9			0.7					
				1/10	42	096	1.8				27.9	185.2*
				1/13	42	089	8.1					
				1/16			8.0					
				1/21	67	152	7.4					
				1/24	76	20	3.4					
				1/28	77	192	1.8				4.9	
				1/31	77	206			5.0		4.5	1143.6
				2/4	80	212						
				2/8			0.65					
				2/11							0.4	
				2/12	94	301	0.5					92.7
				2/19	89	293					Trace	
				2/26	97	328						
				4/5	121	364						Trace (Single specimen only)
Permeious anemia (8)	M	75	180	5/1	44	098	0.27					
				5/3							10.9	
				5/4	38	089	0.85		11.7	0	11.7	
				5/6								535.2
				5/9	39	094	2.6				4.25	
				5/10							6.9	
				5/12			10.1				18.2	
				5/15	49	137	13.8				7.45	325.6
				5/16							13.2	
				5/18							28.1	
				5/19	54	15	9.8				32.4	
				5/20	60	19	9.4					
				5/24							21.0	
				5/26	66	215	1.7				5.6	
				5/28							1.5	
				5/29	77	235	0.9				0.4	
				5/30							0.9	
				6/3	107	32	1.1				Trace	
				6/5							Trace	
				6/9	109	339	0.5					
Probable mild con- genital hemolytic jaundice	F	36	120	12/5	146	468		Faint	8.3	0	0.9	
				12/8				Delayed			2.7	234.1
Mild encephalitis lethargica	F	21	157	12/22	145	438				0	2.05	142.4
Hypertension and polycythemia (Gaisboek ?) after treatment with phenyl- hydrazine	F	53	120	1928								
				10/15	162	540						
				1929								
				8/14	185	685						
				8/23	203	648	0.6					
				8/26	185	626						
				8/31	161	518						
				12/10	172	528		Phenylhydrazine	intermittently			
				12/19	190	534						
				12/27	160	548						
				1930								
				1/20	150	371						
				3/7	184	606						
				4/18	155	485						
				4/24				Weak	9.9	0	0.95	343.8
				4/28	158	492		and indirect				

* Relatively very small amount of stool in four day collection

Urobilinogen Elimination and Other Laboratory Observations—Continued

Diagnosis	Sex	Age	Weight	Date	Hemo- globin	Red Blood Cells	Reticulo- cytes, per Cent	Van Berg's Index	Urine, Bilirubin	Urine, Urobilin	Stool, Urobilin
Chronic chole- cystitis (1)	M	27	160	2/ 6 2/17	16 8	5 02	0 25	9 3	0	0 9	301 5
Chronic chole- cystitis (2)	M	47	155	2/ 6 3/ 9	14 2	4 07			0	1 0	190 2
Chronic chole- cystitis (3)	F	36	140	3/15 3/18	13 9	3 99		Delayed 3 0	+	0 65 (48 hour col- lection only)	633 6
Chronic chole- cystitis (4)	F	45	150	3/ 4	13 6	3 60		8 0	0	7 25 (48 hour col- lection only)	50 6
Chronic chole- cystitis (5)	F	56	210	3/19	16 0	4 89	0 5		0	1 07	226 2
Chronic chole- cystitis (6)	F	58	150	1/17 1/24	Acute exacerbation with fever				0	23 6 2 8	194 3 82 2
Chronic chole- cystitis (7)	M	50	165	2/ 3 3/ 3	16 6	4 70			0	Trace	208 1
Catarrhal jaun- dice (1)	F	16	110	4/ 3 4/ 5 4/ 7 4/12 5/28 5/30	14 1	4 29	0 86	Bipha- sic delayed	52 0 Trace 0 0	69 0 16 8 2 65 (48 hour col- lection only)	221 3
					Symptoms and jaundice subsiding						
					Feels well, no jaundice						
					Recurrent deep jaundice						
Catarrhal jaun- dice (2)	F	12	70	/ 5 3/19 3/21 3/26 3/30 7/ 1	15 8	4 99	2 1	17 0	+	26 5 16 7	255 5
					Symptoms and jaundice subsiding						
					Delayed						
					Jaundice has disappeared				0	1 2	
					Feels well, no jaundice				0	0 6	
Catarrhal jaun- dice (3)	M	47	150	11/ 1 11/ 8 11/ 9 11/10 11/11 11/12 11/13 11/15 12/ 1 12/ 2 12/ 3 12/ 4 12/ 7 1/ 4 7/15	16 1	4 3		Biphasic prompt		4 5* 2 0 21 4 1 9 2 9 4 0	6 9* 12 7 10 4 7 2 9 0
					Cholecystotomy						
									Average	8 46	9 24
									+	61 2*	
									+	46 0	
									+	39 0	
									+	28 4	
									5,		
									Average	43 6	38 5
									25	0	
					Condition good				0	2 09	174 5
Pregnancy (1)	F	34	150	2/18 2/24	10 9	3 16	2 8		0	1 2	152 0
					Mild vomiting of pregnancy symptoms have subsided after 2 weeks in hospital						
Pregnancy (2)	F	36	220	1/ 9 1/12 1/17 1/20 1/21 4/14 4/18	11 8	3 46		Biphasic	90 0		
							2 2			109 8	555 1
					11 9	3 89					
					One week after delivery			15 0		6 9	286 2
					12 7	3 96	0 67	6 9		1 4	150 5
Probable cirrhosis of the liver	M	57	185	5/19 5/23 5/25 5/29 5/31	10 1	2 86		Indirect weakly positive	12 2	10 1*	
									0	1 87 2 7*	633 7
										4 32	170 7

* Forty eight hour collection

lated to some extent with the figures for the cases represented in the table

Probable Mild Congenital Hemolytic Icterus—The patient had always had a dark, sallow skin. Anemia was noted by a physician fifteen years before. None of the patient's relatives had ever had jaundice or a large spleen, so far as was known. There was some dull aching pain in the left upper part of the abdomen. On inspiration, the spleen was felt 1.5 cm. below the margin of the rib in the left midclavicular line. There were 10,000 leukocytes, 62 per cent neutrophils and 35 per cent eosinophils. Moderate anisocytosis with definite predominance of smaller hyperchromatic erythrocytes was noted. In the fragility tests, hemolysis began at 0.46 per cent and was complete at 0.34 per cent, in a control experiment it began at 0.44 per cent and was complete at 0.34 per cent. (Hemolysis of the patient's cells was much more complete between 0.44 per cent and 0.38 per cent than in control.) The Wassermann reaction was negative.

Chronic Cholecystitis—CASE 1—The patient suffered from a distress suggestive of a chronic disease of the gallbladder. He had had typhoid fever fifteen years before. The present symptoms dated to vaccination for typhoid three years before, following which the patient was quite ill and lost considerable weight. Brown pigmentation of the skin, more marked on the unexposed surfaces, appeared at intervals, but it never disappeared entirely. The Graham-Cole test was negative.

Possibly the increased urobilinogen in the stool in this instance is to be explained by a persistent typhoid infection, unfortunately, stools and urine were not examined for typhoid bacilli.

CASE 2—Cholecystectomy was performed. The gallbladder exhibited a mild chronic cholecystitis. Postoperative pneumonia developed, and the patient died. The liver exhibited no evidence of disease at necropsy other than mild cloudy swelling.

CASE 3—The patient suffered from a colicky pain in the right upper quadrant of the abdomen two years before, with jaundice. Severe colic of several days' duration with jaundice occurred in the present attack. The pain had disappeared, and jaundice was definitely lighter at the time of the urobilin estimations. The Graham-Cole test showed a pathologic gallbladder.

Mueller first observed the definite increase of urobilinogen in the stools after release of an obstructive jaundice, whether catarrhal or otherwise. This was quite definite in this instance and was also observed in the cases of catarrhal jaundice. The urobilinogen in the urine was not increased, this coincides well with the view of Wallace and Diamond, who believed that urobilinuria occurred with jaundice due to disease of the liver, not with that due to simple extrahepatic obstruction. The foregoing case is the only instance in the present series which bears on this point. Experimentally, Elman and McMaster found urobilinuria promptly after obstruction of the common duct. More clinical study is necessary to determine the value of urobilinuria in the differentiation of these two divisions of jaundice, i.e., extrahepatic and hepatic obstructive jaundice. Compared with catarrhal jaundice, believed to be of the latter type the foregoing case points to the value

of urobilinuria in differentiation, since cases of catarrhal jaundice, when clearing up present marked urobilinuria

CASE 4—The patient had had repeated gallbladder colics in the past twenty-five years. The present attack was much more severe. At first there were 39,000 leukocytes. The abdomen was distended, very tender, with some rigidity (lower part of the abdomen as well as above). The temperature varied from 102 to 103 F. There was improvement after several days of supportive therapy. The temperature was normal. The amount of urobilin was estimated at this time. A very small amount of stool was obtained. Extensive fat necrosis was found at laparotomy, a markedly diseased gallbladder that contained stones was removed. The convalescence was very difficult and prolonged.

The urobilinuria in this instance was believed to be due to toxic injury to the liver.

CASE 5—Cholelithiasis and pathologic gallbladder were diagnosed by the Graham-Cole method. Repeated colics, occasionally with jaundice, had occurred in the past twenty years. Cholecystectomy was performed, and the liver was found to be apparently normal.

In this case, the moderately increased urobilin in the stool is unexplained either the size of the patient or possibly the mild increased destruction of the blood secondary to infection is to be considered.

CASE 6—The patient had had recurrent gallstone colic, and acute exacerbation with severe pain and rigidity in the right upper quadrant, the temperature was 103. There were 20,800 leukocytes. A Graham-Cole roentgenogram made previously suggested pathologic gallbladder. Estimations of the urobilinogen were made at this time and again after improvement following rest in bed and supportive measures. The temperature was normal, the pain ceased.

This illustrates the effect of acute infection on the liver. The relatively small amount of urobilinuria persisting after the temperature became normal probably indicates mild residual injury to the liver. At laparotomy at this time the gallbladder still contained considerable purulent exudate and was only drained. The liver showed no evidence of disease.

CASE 7—Cholecystectomy was performed, and a moderately diseased gallbladder found. The liver was normal in appearance. Convalescence was rapid.

Catarrhal Jaundice—CASE 1—The patient had had mild jaundice of five days' duration, which was subsiding when seen at the time of the first examination, the symptoms were also disappearing (nausea and vomiting, anorexia and constipation). The stools had been light colored at the onset of the jaundice. At the time the patient was seen the increased urobilin in the stool and marked urobilinuria with the stool-urine ratio of 5:1, permitted a diagnosis of injury to the liver in the stage of recovery. The patient went home apparently quite recovered. It is important to note that the urobilin in the urine was still abnormally elevated, in spite of the apparent complete recovery. The patient returned in six weeks with deep jaundice, at this time the amount of urobilin in the stool and urine were

both low, but the ratio was about 1:1, indicating severe damage to the liver. The stools were clay-colored. The patient was much more ill than previously. The temperature rose daily to 101 and 102 F. There was no pain, but terminal vomiting and a hemorrhagic tendency were present. The patient was toxic and irrational. She died in coma. Permission for necropsy was refused. The clinical diagnosis was subacute yellow atrophy.

CASE 2—The first estimations of the urobilin were made when the symptoms and jaundice were subsiding. Again the urobilinogen in the stool was increased, and the stool-urine ratio was low, about 1:1, indicating injury to the liver. With complete subjective recovery and disappearance of jaundice, the urobilinogen in the urine was normal. This patient was entirely healthy four months later.

CASE 3—The patient was admitted to the hospital on Nov. 1, 1929. Painless jaundice had been present for three weeks. There were anorexia and mild constipation. Fifteen years before the patient had had epigastric distress of two weeks' duration without jaundice. When admitted he had deep jaundice. The edge of the liver was 5 cm. lower than normal, smooth and firm. The stools were clay-colored. The contents of the stomach showed free hydrochloric acid 54, and occult blood was present. Occult blood was found in several stools. A roentgenogram of the gastro-intestinal tract showed a defect typical of a small duodenal ulcer. Leucine and tyrosine were absent in two urinalyses, but were present on the third examination with correct solubility tests. Bromsulphalein retention was 45 per cent in thirty minutes, iso-iodoikon showed 40 per cent retention, the gallbladder was poorly visualized. Operation was preceded by daily administration intravenously of dextrose and calcium chloride. At laparotomy, the liver was found enlarged, swollen, and reddish, there were few adhesions around the gallbladder and a definite small duodenal ulcer. No obstruction to the common duct was found. The gallbladder was drained. There was considerable drainage of dark bile subsequently, followed by definite improvement. Modified Sippy ulcer management was begun. On Jan. 3, 1930, the patient was up and about and felt very well. The liver was not palpable, and there was only very slight skin jaundice. The total duration of the jaundice was about three months. On July 15 the patient's condition was good, and there had been no recurrence of jaundice.

The very low stool-urine urobilinogen ratio (about 1:1), persisting for some time even after partial resumption of the flow of bile, indicated severe injury to the liver. This, with the long duration of the jaundice and the occurrence of leucine and tyrosine in the urine, necessitated a poor prognosis. Recovery was believed to be aided by the intravenous administration of dextrose and drainage of the gallbladder; whether the drainage of bile was due to coincidental beginning recovery or to a suction action on the liver, remains a mystery. Following the disappearance of jaundice, a practically normal stool-urine ratio is noted, with urine urobilinogen still slightly increased.

Pregnancy—CASE 1—The patient, pregnant about four months, had mild toxic vomiting with secondary anemia. Estimations of the urobilinogen were made after ten days of hospitalization, with considerable improvement.

CASE 2—The patient was seven and one-half months pregnant. She suffered from moderate jaundice, daily colicky pain in the right upper quadrant and vomiting. There was no fever. She had had similar attacks previously. The gall-

bladder was drained two years before while she was seven months pregnant, she did not think that stones were found. Moderate albuminuria was present. There were 5,850 leukocytes, 71 per cent neutrophils, and moderate anisocytosis. Immediate marked improvement followed spontaneous labor.

In spite of the probable existence of disease of the gallbladder in this instance and the possibility of a stone in the common duct, the estimations of urobilinogen pointed to increased destruction of the blood borne out by the regenerative anemia and to considerable injury of the liver because of the low stool-urine ratio. This approached normal soon after delivery. It was believed that the observations could be explained on the basis of a toxemia of pregnancy.

Pernicious Anemia—CASE 1—The disease was recognized one year prior to the patient's admission to the hospital. Liver extract in relatively small doses was given during the last eight months. There were definite numbness and tingling of the extremities. The patient did not have "sore tongue." No free hydrochloric acid was found in the contents of the stomach. Erythrocytes showed marked macro-anisocytosis and hyperchromasia. There were 4,200 leukocytes and 44 per cent lymphocytes. The neutrophils exhibited a moderate shift to the right. The color index was 1.5. Intensive liver therapy was begun on Nov. 27, 1929, with only moderate response. The patient left the hospital against advice on December 12. The condition was said to be unimproved four months later, blood smears showed definite macro-anisocytosis.

CASE 2—Weakness, yellow skin, sore tongue, numbness and tingling had been noted in the past year. The tongue was smooth. There was a loud blowing systolic murmur at the apex of the heart. The erythrocytes showed marked hyperchromasia and macro-anisocytosis. There were frequent "pernicious anemia" neutrophils. Occasional normoblasts were seen at times with multiple nuclear buds, there were occasional myelocytes, 6,250 leukocytes and 67 per cent neutrophils. The patient was extremely weak and suffered from fever and vomiting. Liver extract equivalent to about 800 Gm. of liver was given by rectum. The patient died three hours after a transfusion of 500 cc. of citrated blood. Necropsy showed marked arteriosclerosis with extensive coronary thickening and some fibrosis cordis. Deeply pigmented bile was seen in the gallbladder. The liver showed no gross disease. The spleen weighed 300 Gm., and was firm and dark red. The bone-marrow shaft of the femur was definitely hyperplastic (red). Microscopic examination showed an occasional hypertrophic Kupffer cell, with infrequent erythrophagocytosis, very little hemosiderin, markedly hyperplastic bone-marrow approximately equally myeloblastic and erythro-megaloblastic, diffuse pulp congestion in the spleen and slight hemosiderosis.

CASE 3—The patient had had epigastric distress suggestive of peptic ulcer for the past several months, weakness, some numbness and tingling in the extremities for two months, a smooth tongue, pale yellowish skin and impaired sense of vibration. Examination of the blood showed marked macro-anisocytosis, dispersion of the Arneeth count to the right and left, with occasional typical neutrophils, 2,500 leukocytes with 43.5 per cent lymphocytes and 5 per cent eosinophils. There was no free hydrochloric acid. Marked improvement followed intensive liver therapy (500 Gm. of cooked liver daily).

CASE 4—The patient had had weakness, sore tongue and substernal pain for two years. Definite macro-anisocytosis, poikilocytosis, slight polychromasia and occasional normoblasts were noted. There was no free hydrochloric acid. Improvement of blood was shown after daily administration of liver extract equivalent to 500 Gm of liver. There was considerable subjective improvement.

CASE 5—The patient had had pale yellow skin varying in degree for the past two years. A sore tongue and mouth, weakness and dyspnea had been present for the past year. Numbness and tingling were felt in the extremities for the past few weeks. Erythrocytes showed hyperchromasia, macro-anisocytosis and marked poikilocytosis. There were occasional normoblasts, myelocytes and promyelocytes, with 2,600 leukocytes and 41.5 per cent lymphocytes, and later 5,600 leukocytes and 37 per cent lymphocytes. Definite "pernicious anemia" neutrophils were present. Liver or liver extract equivalent, 500 Gm, daily was given (beginning March 6, 1930). On June 21, the patient felt quite well, and had a good appetite.

CASE 6—The patient complained of dyspnea, weakness and sore tongue. There were 3,650 leukocytes and 46.5 per cent lymphocytes, the neutrophils showed a marked shift to the right. Marked macro-anisocytosis and hyperchromasia and some poikilocytosis were present. The Minot-Murphy diet was begun on Jan 11, 1930 (500 Gm of liver daily), and caused marked improvement. On April 4, the patient's condition was good. The liver therapy was continued (from 200 to 300 Gm daily).

CASE 7—The patient suffered from progressive weakness and dyspnea for one year. The skin was pale and yellowish. There were 4,350 leukocytes and 49 per cent lymphocytes. The neutrophils showed a shift to the right. Marked hyperchromasia and macro-anisocytosis, and poikilocytosis were present. There were occasional normoblasts, some with multiple nuclear buds. Liver extract, equivalent to from 400 to 500 Gm of liver, was given daily. Later, this therapy was supplemented by cooked whole liver. On April 5, 1930, the patient felt fairly well but was still somewhat weak. The blood has improved as shown.

CASE 8—The patient was extremely weak and irrational, with pale yellow skin and a moderately smooth tongue. There were 2,750 leukocytes with 57.5 per cent lymphocytes, 8 per cent eosinophils. The erythrocytes showed marked macro-anisocytosis, poikilocytosis and hyperchromasia. There were frequent normoblasts with multiple nuclear buds, some basophilic stippling and occasional "pernicious anemia" neutrophils. Liver extract equivalent to from 400 to 500 Gm of liver was given daily, with some difficulty. There was considerable improvement. The patient left the hospital on June 9, 1930.

The repeated estimation of urobilinogen in the foregoing cases of pernicious anemia in which liver therapy was used suggested that they could be divided into two groups in which the absence or persistence of urobilinuria after the reticulocyte crisis was correlated with the rate of increase of erythrocytes and hemoglobin. Patients in whom urobilinuria disappeared at or before the reticulocyte crisis (cases 3, 4 and 6 in table) exhibited an increase of hemoglobin over a considerable period at the average rate of 0.143 Gm per day and of 0.055 millions of erythrocytes per day while those in whom urobilinuria persisted for even a short time after the reticulocyte crisis (cases 5, 7 and 8) the

corresponding values were 0.120 and 0.048. Case 1 was not included in the latter group, because the patient had been on liver therapy for a much longer period, and was therefore not comparable. It was significant, however, that while his blood failed to show improvement, urobilinuria was definite, with normal urobilin in the stool.

In these two groups the average elevation of hemoglobin reached in the first (with disappearance of urobilinuria) was 14.2 Gm. and of red blood cells 3.99 millions, this was observed after an average period of forty-seven and seven tenths days. Corresponding values in the second group were 10.7 and 3.56, over an average period of observation of forty-two days. The slight variation in time is not enough to account for the discrepancy, at least as regards the hemoglobin, where correction for the five and seven tenths days brings the value only to eleven and four tenths, while the erythrocyte average corrected is three and eighty-three hundredths. This suggests some interference in the formation of hemoglobin in the second group. It is realized that the number of cases is too small to permit definite conclusions.

The average value for urobilin in the stool in relapse was 557.7 Gm., and in remission induced by liver therapy it was 183.6. This observation, of course, suggests that liver acts by curtailing the increased destruction of the blood. This is the view of Basch, Jungmann, Dyke and Greener, and Schulten. Nothing is known of the factor of urobilin resorption in pernicious anemia, and possibly it is reduced in relation to the fairly constant gastro-intestinal pathologic changes. However, the fact that urobilinuria may often be considerable, as in the present series, is against this conception.

No relation was found to exist between the amounts of urobilinogen in the stool and urine. The urobilinogen in the urine might be increased with a low amount of urobilinogen in the stool as in the first case, or low with a high stool value as in cases 2 and 3. This, obviously, did not support the simple "overflow" theory. Because of the well recognized relation of injury to the liver to urobilinuria and the definite anatomic variations in the liver in relapse and remission, as recently shown by Mettier, together with the present observations, it is suggested that in pernicious anemia urobilinuria is only an evidence of liver derangement.

SUMMARY

Knowledge of the average daily elimination of urobilinogen is often of great aid in the clinical study of jaundice and anemia. This may be obtained by use of the modification of Terwen's method, described herein. The method is not difficult, although any quantitative method applied to feces is necessarily time-consuming. Standardization of the colorimetric procedure is based on the color produced by a chemical individual mesobilirubinogen, when condensed with paradimethyl-

aminobenzaldehyde by means of hydrochloric acid. This method gives slightly higher values than the original technic of Terwen's. The average urobilinogen in the normal stool was considered by Terwen to be 134, compared with 151.2 in the present series, while the average figures for pernicious anemia are respectively, 455.3 and 554.7 (relapse only). Values for urobilinogen in the stool were found reduced in secondary anemia, unless regenerative with increased destruction of the blood when they were higher. The urobilinogen in the stool was increased for a short time after release of obstructive jaundice, and the stool-urine ratio was reduced with injury to the liver. In pernicious anemia, the rate of increase of hemoglobin and red blood cells in patients treated with liver therapy was somewhat slower if urobilinuria persisted beyond the reticulocyte crisis. Urobilinuria was believed not simply due to overflow with a normal liver but probably to an actual derangement of the liver, more marked in some instances than others.

CONCLUSIONS

1. A modification of Terwen's method for the estimation of urobilinogen in urine and feces is described, which is believed to be simpler and more efficient than the original procedure.

2. Standardization of the color standard is based on crystalline mesobilirubinogen (Fischer).

3. Results of a series of cases studied with this method are reported and indicate that valuable information may be obtained by its use in the clinical study of jaundice and of the anemias.

4. Persistent urobilinuria after the reticulocyte crisis in cases of pernicious anemia in which liver therapy is used is accompanied by a slower rate of increase of hemoglobin and, to a less marked degree, of erythrocytes.

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CENTRAL VASOMOTOR IRRITABILITY

CONTRIBUTION TO THE PROBLEM OF ESSENTIAL HYPERTENSION *

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In a previous paper¹ there was described a characteristic feature of essential (not nephritic) hypertension, namely, an increased sensitivity of the vasomotor centers to changes in alveolar carbon dioxide tension—abnormally high rises of blood pressure during the inhalation of carbon dioxide and an abnormal fall of blood pressure during the increased exhalation of carbon dioxide (hyperventilation, Tirala² and Rappaport³). There is a striking parallelism between the figures of alveolar carbon dioxide and of blood pressure during hyperventilation in hypertonic patients, while a fall of carbon dioxide to the same extent does not change the blood pressure of hyperventilating normal persons in any definite way (Collin, Densham and Wells⁴; Schneider⁵). From this characteristically different behavior of normal and hypertonic persons the conclusion has been drawn that a pathologic hypersensitivity of the vasomotor centers (not only to abnormally high amounts of carbon dioxide but even to the normal carbon dioxide content of the blood) may be an important factor contributing to the high blood pressure level in hypertonic persons. Carbon dioxide acts, as is well known, as a specific stimulant on the central vasomotor apparatus. Henderson⁶ said: "Carbon dioxide tension in the nerve centers is a factor in the maintenance of tonus." Furthermore, it has recently been shown by Weiss and Ellis⁷ that the increased blood pressure in hypertension is due to a contraction of the peripheral vessel system and not to primary changes in the general blood volume, cardiac output,

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1 Raab, W. *Ztschr f d ges exper Med* **68** 337, 1929

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3 Rappaport, Israel. Blood Pressure and Respiration. Hyperventilation as a Treatment for Hypertension. *J A M A* **92** 1158 (April 6) 1929

4 Collin, Densham and Wells. *Quart J Exper Physiol* **18**:291, 1927

5 Schneider, E. C. *Am J Physiol* **91** 390, 1930

6 Henderson, Y. *Am J Physiol* **24** 65, 1909

7 Weiss and Ellis. *Am Heart J* **5** 635 (June) 1930

circulation through the lungs or velocity of the blood flow. This also suggests a dominant rôle of the vasomotor centers in hypertension.

The question arose, What is the cause of that hyperirritability, and by what means would it be possible to imitate similar conditions experimentally in animals? Many outstanding investigators attribute an essential importance for the genesis of hypertension to central nervous factors (von Monakow,⁸ Krehl,⁹ Pal,¹⁰ Goldscheider,¹¹ Kahler,¹² A. Loewy,¹³ Cobet,¹⁴ etc.) Emphasis has been put on the frequent presence of arteriosclerotic alterations of the vessels of the brain (Riebold,¹⁵ Lippmann,¹⁶ Munk,¹⁰ and others). A thorough histologic study of the latter subject has recently been published by Bordley and Baker¹⁷ concerning twenty-four cases of arteriosclerosis in fourteen of which the patients had suffered from doubtless hypertension while in ten the blood pressure had been normal. The authors found sclerotic alterations in the walls of the vessels of the medulla oblongata in the hypertonic patients but not in those with normal blood pressure. It is true that Cutler¹⁸ observed conditions of the kind mentioned in only about 25 per cent of eighteen brains from hypertonic persons, but on the other hand the possibility of spastic contractions even of the vessels of the brain not leaving any anatomic traces has frequently been emphasized. Finally, it may be mentioned that a rise in blood pressure can also be caused by an increase of intracranial pressure (Cushing,¹⁹ Kahler¹² and others). All investigators unanimously assume the diminishing of the supply of blood and oxygen to be the essential moment in the importance of all of the different conditions for the increased tonus of the vasomotor centers. Experimental evidence for this conception has been given by Mathison²⁰ and Anrep and Starling,²¹

8 von Monakow, P. *Deutsches Arch f klin Med* **115** 47 and 224, 1914, **133** 1983, 1920.

9 Krehl, in von Mering, J. *Lehrbuch der inneren Medizin*, ed 13, Jena, Gustav Fischer, 1921.

10 Quoted by Kahler. *Ergebn d inn Med u Kinderh* **25** 265, 1924.

11 Goldscheider. *Ztschr f phys u diätet Therap* **23** 25, 1919, **25** 1, 1921.

12 Kahler. *Ergebn d inn Med u Kinderh* **25** 265, 1914.

13 Loewy, A. *Arch f d ges Physiol* **207** 632, 1925.

14 Cobet. *Biochem Ztschr* **137** 67, 1923.

15 Riebold. *München med Wchnschr*, 1917, vol 43.

16 Lippmann. *Deutsche med Wchnschr* **44** 907, 1918.

17 Bordley, J. III, and Baker, B. M., Jr. *Bull Johns Hopkins Hosp* **38** 320, 1926, **39** 229, 1926.

18 Cutler, O. I. *Relation of Arteriosclerosis of Cerebral Vessels to Hypertension. Distribution of Arteries Supplying the Pons and Medulla*, *Arch Path* **5** 365 (March) 1928.

19 Cushing. *Bull Johns Hopkins Hosp* **12** 290, 1901.

20 Mathison. *J Physiol* **41** 416, 1910, **42** 283, 1911.

21 Anrep and Starling. *Proc Roy Soc Med* **97** 463, 1924.

as well through artificial reduction of the circulation of the brain, as by cutting down the respiratory oxygen supply, furthermore Gurdjian produced strong increases of blood pressure by the application of sodium cyanide to the medulla oblongata, which prevents oxidation

Lack of oxygen causes an accumulation of lactic acid not only in the muscles (Fletcher and Hopkins,²³ etc.) but also in the nervous (Fenn,²⁴ Gerard²⁵) and brain tissue (McGinty and Gesell,²⁶ Cobet²⁷) especially in the medulla oblongata (Haldi, Ward and Woo²⁸) On the other hand it is known that acids generally stimulate the vasomotor centers (Traube,²⁹ Mathison³⁰ Bainbridge,³⁰ Itami,³¹ Cobet,¹⁴ Eppinger, Kisch and Schwarz,³² Gesell,³ Gollwitzer-Meier³⁴ and others) In regard to those facts it is not too far fetched to imagine that even the clinical hypertonic blood pressure might be at least partly due to an accumulation of acid substances, especially of lactic acid within the region of the vasomotor centers as a consequence of local circulatory disturbance and thus a diminished oxygen supply, an idea that has already been suggested by Cobet,¹⁴ Lichtwitz³⁵ and A. Loewy¹³ (Straub and Meier³⁶ and von Romberg³⁷ have applied the same conception to the respiratory center for explaining "central dyspnea")

This hypothesis being logically well enough founded it seemed worth while to search for experimental evidence It was considered as a suitable procedure in this direction to examine the effect of a diminished supply of oxygen and of artificial acidification of the centers concerning not only the sufficiently well studied plain rise of blood pressure but mainly the degree of irritability under those conditions In other words, Do the shortage of oxygen and the presence of lactic acid in the vaso-

22 Gurdjian, E. S. *Am J Physiol* **82** 261, 1927

23 Fletcher and Hopkins. *J Physiol* **35** 247, 1907

24 Fenn, W. O. *Am J Physiol* **80** 327, 1927

25 Gerard, R. W. *Am J Physiol* **82** 381, 1927

26 McGinty, D. A., and Gesell, R. *Am J Physiol* **83** 323, 1927

27 Cobet. *Arch f exper Path u Pharmacol* **145** 140, 1929

28 Haldi, J. A., Ward, H. P., and Woo, L. *Am J Physiol* **83** 250, 1927

29 Traube. *Gesammelte Abhandlungen*, Berlin, A. Hirschwald, 1856 vol 2

30 Bainbridge, F. A. *J Physiol* **54** 192, 1920-1921

31 Itami. *J Physiol* **45** 338 1912-1913

32 Eppinger, Kisch and Schwarz. *Das Versagen des Kreislaufes*, Berlin Julius Springer, 1927

33 Gesell, R. *Ergebn d Physiol* **28** 340, 1929

34 Gollwitzer-Meier, K. *Arch f d ges Physiol* **222** 104 and 124, 1929

35 Lichtwitz. *Die Praxis der Nierenkrankheiten*, Berlin, Julius Springer, 1925, quoted by Blum, R. *Ergebn d inn Med u Kinderh* **35** 255, 1929

36 Straub, H. and Meier, K. *Deutsches Arch f klin Med* **138** 208 1922

37 von Romberg, E. *Wien med Wchnschr* **80** 361 1930

motor centers produce besides an irritation of the centers an increased irritability which is an important characteristic of essential hypertension? Evidence for hyperirritability in hypertonic men has been given by the reactions to changes of alveolar (blood) carbon dioxide, as mentioned, and by the sudden abnormally high rises of blood pressure due to peripheral stimuli, especially to pain (Cuischmann,¹⁰ Pal,³⁸ Kahler,¹² Eisenfarb³⁹ and others) and to psychic emotions (Kulbs,⁴⁰ Ayman⁴⁴ and others)

A general increase of nervous excitability under the influence of a shortage of oxygen and under the action of acids has been reported by various authors (Bethe,⁴² Syz,⁴³ Boehm,⁴⁴ Batelli,⁴⁵ Elias,⁴⁶ Winterstein,⁴⁷ Kaya and Starling⁴⁸ Brailsford-Robertson⁴⁹ and others) Haldane and his collaborators⁵⁰ observed an increased sensitivity of the respiratory center to carbon dioxide through the diminution of oxygen Gesell³³ assumed that the respiratory center is more sensitive to carbon dioxide the less it is buffered Cobet⁵¹ and Mosler⁵² observed a stronger increase of blood pressure in hypertonic than in normal persons if the supply of oxygen was cut down Mathison²⁰ found a summation of the effects of the infusion of acids and the inhalation of carbon dioxide in decerebrate cats He also discussed the possibility that the lack of oxygen caused an "intraneural" formation of acids in an amount sufficiently high to excite the vasomotor centers but not to be detected in the circulating blood

The fact that painful peripheral stimuli cause a rise in blood pressure has been stated by Heidenhain,⁵³ Bradford,¹⁰ Tigerstedt¹⁰ and others

38 Pal, J Die Gefasskrisen, Leipzig, S Hirzel, 1905, footnote 10

39 Eisenfarb, J Klin Wchnschr **9** 552, 1930

40 Kulbs, in Mohr-Staehelin Lehrbuch der inneren Medizin, ed 2, Munich, J F Bergmann vol 2, p 443

41 Ayman, D Normal Blood Pressure in Essential Hypertension, J A M A **94** 1214 (April 19) 1930

42 Bethe Ergebn d Physiol **5** 250, 1906

43 Syz J Pharmacol **30** 1, 1907

44 Boehm Arch f exper Path u Pharmacol **8** 68, 1878

45 Batelli J de physiol et de path gen **2** 443, 1900

46 Elias Ergebn d inn Med u Kinderh **25** 192, 1924

47 Winterstein Ztschr f allg Physiol **3** 359, 1903

48 Kaya and Starling J Physiol **39** 346, 1909-1910

49 Brailsford-Robertson Festschrift fur Hamburger, 1905, p 287, quoted by Elias (footnote 46)

50 Haldane and Poulton J Physiol **37** 390, 1908 Haldane and Boycott J Physiol **37** 369, 1908 Douglas and Haldane J Physiol **38** 420, 1909

51 Cobet Deutsches Arch f klin Med **143** 253, 1924

52 Mosler Ztschr f klin Med **78** 133, 1913

53 Heidenhain Arch f d ges Physiol **3** 505, 1870, **5** 77, 1872

It is usually considered as being a reflex phenomenon, although even a discharge of epinephrine from the suprarenals can play a role under certain conditions (Cannon,⁵⁴ Houssay and Molinelli,⁵⁵ Tournade and Chabrol,⁵⁶ and others)

In the following experiments inhalation of carbon dioxide, hyperventilation and electric stimulation of the cranial nerve have been used as tests for the excitability of the vasomotor centers under various conditions

Finally, there exists a rather characteristic feature in essential hypertension in man—a frequently reverted or at least weakened response of the blood pressure to epinephrine (Schlesinger and Arnstein,⁵⁷ Dresel,⁵⁸ Jansen,⁵⁹ Kaufmann,⁶⁰ Kylvn,⁶¹ Basch,⁶⁰ and others) Intravenous injections of epinephrine have therefore also been used as a test for experimental hypertonic conditions

TECHNIC

In all of the experiments, cats decerebrated under ether anesthesia have been used because the reactivity of the vasomotor centers had been found to be too much injured by continuous anesthesia (von Esveld⁶²) The vagi on the left and the right sides were cut

Registration of the blood pressure was done with a mercury manometer partly from the femoral artery and partly from the left carotid artery Graphical registration was taken of the intratracheal air pressure

Lactic acid and other substances were injected through a cannula tied into the central stump of the right carotid artery and connected with the syringe by means of a thick rubber tubing By this method the liquid injected reaches the brain stem through the right vertebral artery Longer lasting infusions were made with a special apparatus designed by Dr Magnus Gregersen, to be described subsequently by himself—an electrically driven pinion mechanism which warrants a regular pushing forward of the piston of the fixed syringe with various definite slow speeds

The control analyses of the gas mixtures were made by Miss E Bright A spirometer was inserted between the steel tanks and the respiration valves

For artificial respiration, an air pump constructed by Prof C Drinker was used Its speed could be varied between fifteen and twenty-six revolutions per minute, the single stroke volume being between 0 and 97 cc

54 Cannon *Am J Physiol* **1** 399, 1919

55 Houssay, B A, and Molinelli, E A *Rev Soc argent de biol* **1** 125, 1925

56 Tournade, A, and Chabrol, M *Compt rend Soc de biol* **92** 418, 1925

57 Schlesinger and Arnstein *Wien klin Wchnschr* **49** 1179 1919

58 Dresel *Deutsche med Wchnschr* **45** 955, 1919

59 Jansen, W H *Deutsches Arch f klin Med* **147** 339, 1925

60 Quoted by Kylvn, Eskil *Die Hypertoniekrankheiten*, Berlin Julius Springer, 1926

61 Kylvn, Eskil *Die Hypertoniekrankheiten*, Berlin, Julius Springer, 1926

62 von Esveld *Arch f exper Path u Pharmacol* **147** 297 1930

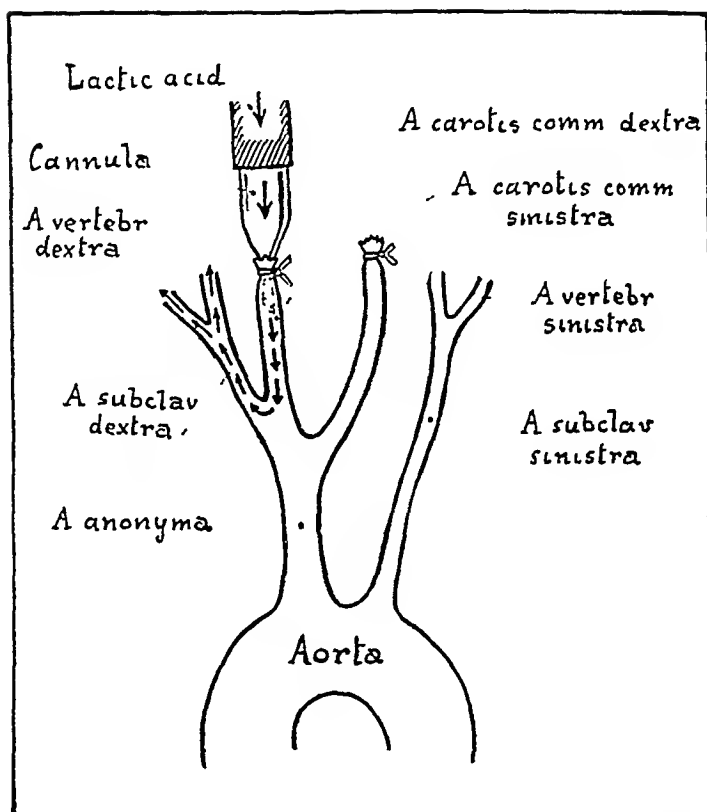


Fig 1—After Reighard and Turnings The Anatomy of the Cat, New York, Henry Holt & Company, 1925

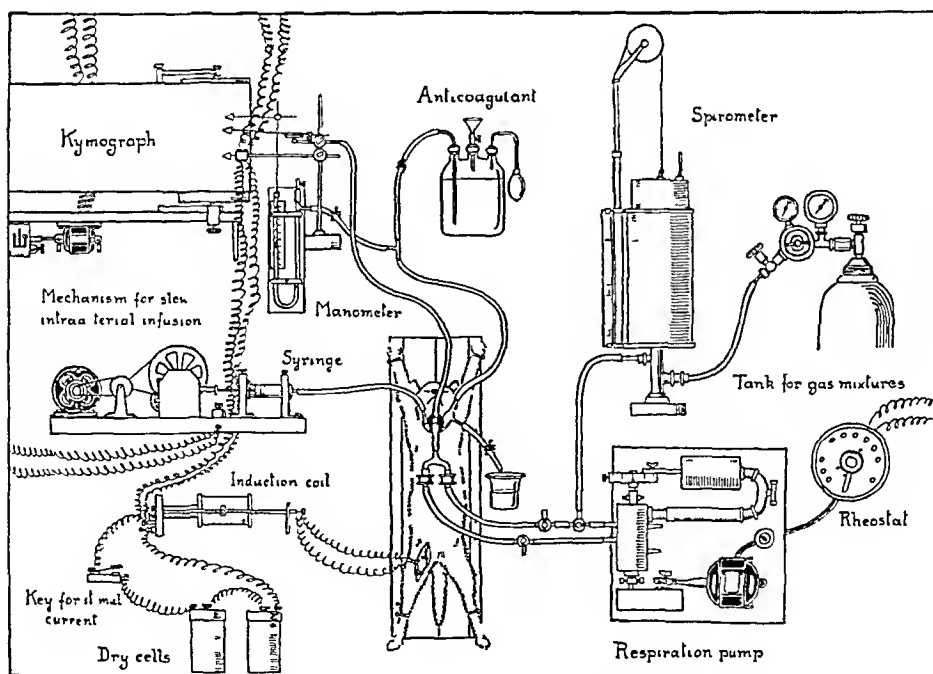


Fig 2—Apparatus used in the experiments

The single periods of the experiments were generally separated by intervals of from ten to thirty minutes to secure sufficient recovery after each period.

The greater number of experiments were done with the maintenance of the spontaneous respiration because a poisoning with curare is not quite indifferent for the mode of reaction of the vasomotor centers (Grützner and Heidenham⁶³ Latschenberger and Deahna⁶⁴ Tillie,⁶⁵ Martin and Stiles⁶⁶) while without paralysis of the breathing muscles, disturbing interferences occur between spontaneous and artificial respiratory movements of the chest.

TABLE 1—*Effect of Carbon Dioxide Together with Want of Oxygen*

Ex- peri- ment	Period of Experi- ment	Gas Mixture Inhaled			Duration of Experi- mental Period, Minutes	Blood Pressure			Comparison of Results
		Carbon Dioxide, per Cent	Oxygen, per Cent	Nitrogen, per Cent		Initial	Maximum Attained	Devia- tion	
1	a	3.6	25	71.4	2	96	115	+19	$b = a + c - 11$
	b	3.6	10	86.4	2	94	120	+36	
	c		10	90.0	2	100	106	+6	
2	a	6.0	25	69.0	2	124	146	+22	$c = a + b + 5$
	b		10	90.0	2	96	106	+10	
	c	6.0	10	84.0	2	94	131	+37	
3	a		10	90.0	2	110	116	+6	$c = a + b + 4$
	b	6.0	25	69.0	2	120	152	+32	
	c	6.0	10	84.0	2	96	138	+42	
4	a	6.0	25	69.0	2	98	86	-12	$c = a + b + 11$
	b		10	90.0	2	92	96	+4	
	c	6.0	10	84.0	2	96	121	+25	
5	a	6.0	25	69.0	2	118	211	+93	$c = a + b + 10$
	b		10	90.0	2	112	139	+27	
	c	6.0	10	84.0	2	102	232	+130	
6	a	3.6	25	71.4	2	164	182	+18	$b = a + c + 6$
	b	3.6	10	86.4	2	162	194	+34	
	c		10	90.0	2	160	170	+10	
7	a		10	90.0	2	132	147	+15	$c = a + b + 59$
	b	3.6	25	71.4	2	116	136	+20	
	c	3.6	10	86.4	2	70	164	+94	

EXPERIMENTS

Combination of Effect of Carbon Dioxide with Want of Oxygen (table 1) —These experiments show without exception an increase of the effect of carbon dioxide on blood pressure if combined with a diminished supply of oxygen. The effect of carbon dioxide with only 10 per cent of oxygen gives a higher rise in blood pressure than the sum of the single effects of carbon dioxide alone and of 10 per cent of oxygen alone.

63 Grützner and Heidenham. *Arch f d ges Physiol* **16** 47, 1878.

64 Latschenberger and Deahna. *Arch f d ges Physiol* **12** 157, 1876.

65 Tillie quoted by Boehm. *Handbuch der experimentellen Pharmakologie* Berlin, V. Heffter 1920 vol 2 p 179.

66 Martin and Stiles. *Am J Physiol* **34** 220 1914.

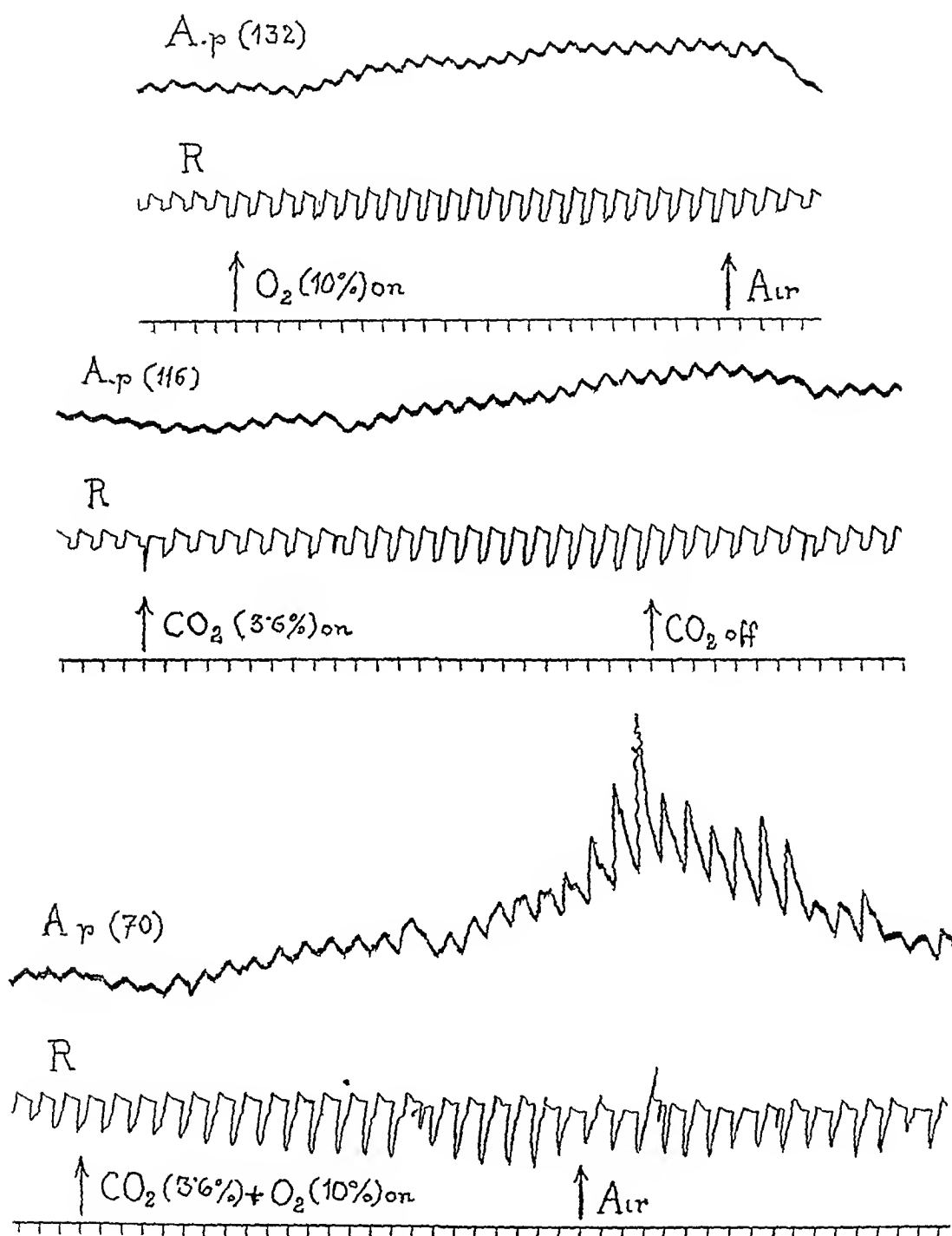


Fig 3 (experiment 7) —Effect of carbon dioxide increased through the want of oxygen

Combination of Effect of Carbon Dioxide with Lactic Acid (tables 2 and 3) —As it had been planned to inject diluted lactic acid into the right carotid artery one had to reckon with the theoretical possibility that the mere dilution of the blood (although being very moderate) could

TABLE 2—*Controls with Saline Solution Injected into the Central Stump of the Right Carotid and the Effect of Carbon Dioxide*

Ex per iment	Period of Ex per iment	Sodium Chloride Infused		Gas Mixture Inhaled			Dura tion of Experi mental Period, Min	Blood Pressure			Comparison of Results
		Concen tration, per Cent	Vol ume, Cc	Carbon Dioxide, per Cent	Oxy gen, per Cent	Nitro gen, per Cent		Initial	Maxi mum Attained	Devia tion	
8	a			3	25	72	2	150	171	+21	a = b
	b	0.9	3	3	35	72	2	154	175	+21	

TABLE 3—*Lactic Acid Injected into the Central Stump of the Right Carotid and the Effect of Carbon Dioxide*

Ex- per- iment	Period of Ex- per- iment	Lactic Acid Infused		Gas Mixture Inhaled			Dura- tion of Experi- mental Period, Min	Blood Pressure			Comparison of Results
		Concen- tration, per Cent	Vol- ume, Cc	Carbon Dioxide, per Cent	Oxy- gen, per Cent	Nitro- gen, per Cent		Initial	Maxi- mum Attained	Devia- tion	
9	a			3.6	25	71.4	2	120	147	+27	c = a+b+24
	b	n/20	3.0		Air		2	112	129	+17	
	c	n/20	3.0	3.6	25	71.4	2	118	186	+68	
10	a			3.6	25	71.4	2	140	178	+38	c = a (re- spectively d)+b+28
	b	n/20	2.5		Air		2	104	104	± 0	
	c	n/20	2.5	3.6	25	71.4	2	72	138	+66	
	d	n/20		3.6	25	71.4	2	46	84	+38	
11	a			6.0	25	69.0	2	132	171	+39	e = a+b+7 d = a+b+18
	b	n/20	3.0		Air		2	110	130	+20	
	c	n/20	3.0	6.0	25	69.0	2	136	202	+66	
	d	n/20	3.0	6.0	25	69.0	2	120	197	+77	
	e	n/20		6.0	25	69.0	2	136	166	+37	
12	a			6.0	25	69.0	2	124	146	+22	b = a+c+64 d = a+c+6
	b	n/20	3.0	6.0	25	69.0	2	90	179	+89	
	c	n/20	3.0		Air		2	90	93	+3	
	d	n/20		6.0	25	69.0	2	96	125	+31	
13	a			3.0	25	72.0	2	114	132	+18	c (150" after b) = a+b+13
	b	n/20	3.0		Air		2	108	135	+27	
	c	n/20	(3.0)	3.0	25	72.0	2 (6)	135 (108)	166	+58	
14	a			3.0	25	72.0	2	150	155	+5	c = a+b+11
	b	n/20	2.0		Air		2	156	148	+12	
	c	n/20	2.0	3.0	25	72.0	2	106	134	+28	
15	a			3.6	25	71.4	2	74	95	+21	c = a+b+27
	b	n/15	2.0		Air		2	60	76	+16	
	c	n/15	2.0	3.6	25	71.4	2	64	128	+64	

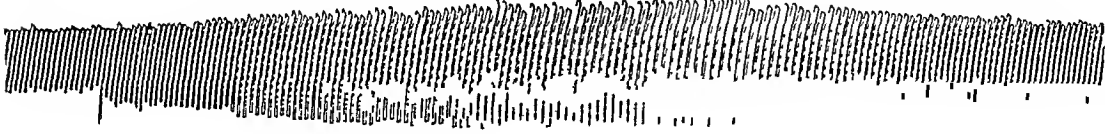
perhaps affect the tonus of the vasomotor centers in consequence of the somewhat diminished oxygen content of the diluted blood. This is, however, not the case, as the control experiment 8 (table 2) shows.

In all of these experiments the effect of carbon dioxide on the blood pressure was increased by the simultaneous (in experiment 13 by previous) injection of lactic acid into the central stump of the right carotid

A_p (74)



R.



↑ CO₂ (36%) on

↑ CO₂ off

A_p (60)



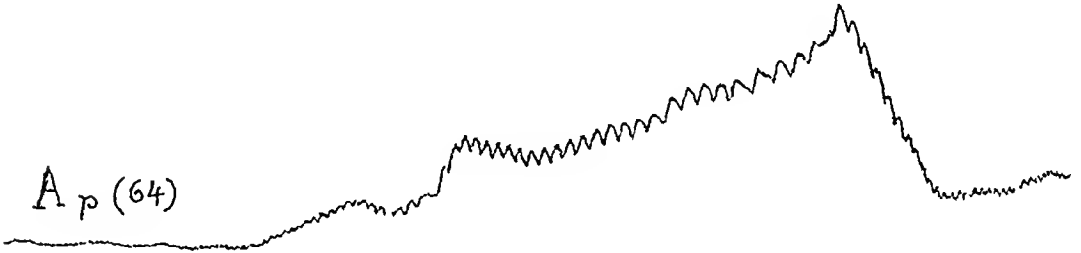
R



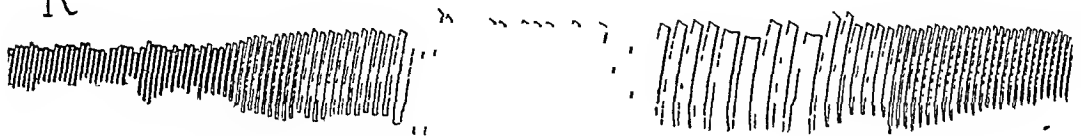
↑ Lact acid ($\frac{n}{15}$, 2 cc) into right carotid

↑ End of inj

A_p (64)



R



↑ CO₂ (36%) on

↑ Lact acid ($\frac{n}{15}$ 2 cc) into right carotid

↑ CO₂ off

↑ End of inj

Fig 4 (experiment 15) —Effect of carbon dioxide increased through the infusion of lactic acid

artery The effect of lactic acid and carbon dioxide combined is considerably higher than the sum of the single effects

Combination of Effect of Carbon Dioxide with Acetic Acid (table 4) —Although acetic acid in the concentration used (twentieth-normal) does not cause an increase but rather a slight decrease of blood pressure, the effect of carbon dioxide in its presence is still intensified

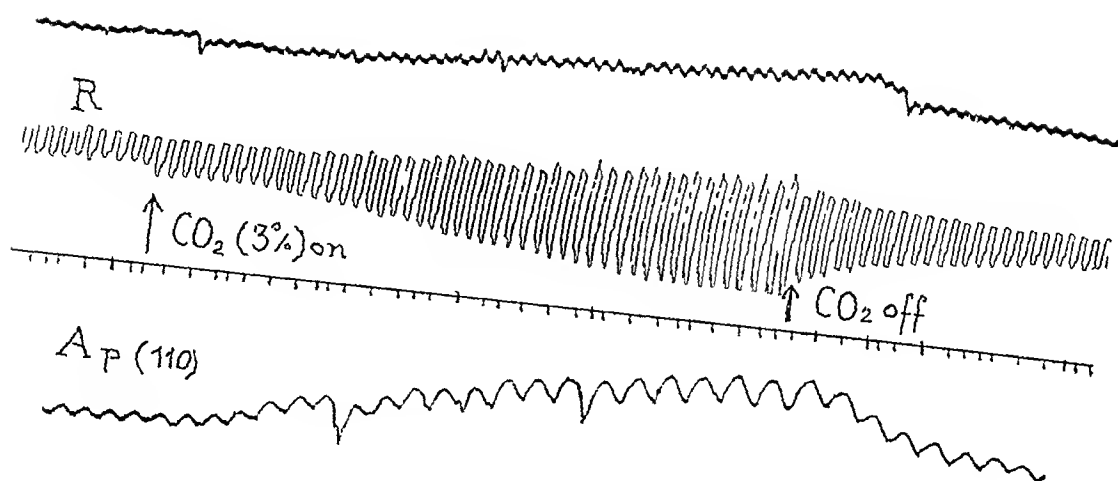
Effect of Carbon Dioxide After Injection of Lactic Acid into the Suboccipital Cavity (tables 5 and 6) —In the following experiments, after having exposed the atlanto-occipital membrane, lactic acid (and as a control physiologic solution of sodium chloride) was injected into the cerebrospinal cavity not far from the region of the vasomotor

TABLE 4—*Acetic Acid Injected into the Central Stump of the Right Carotid and Effect of Carbon Dioxide*

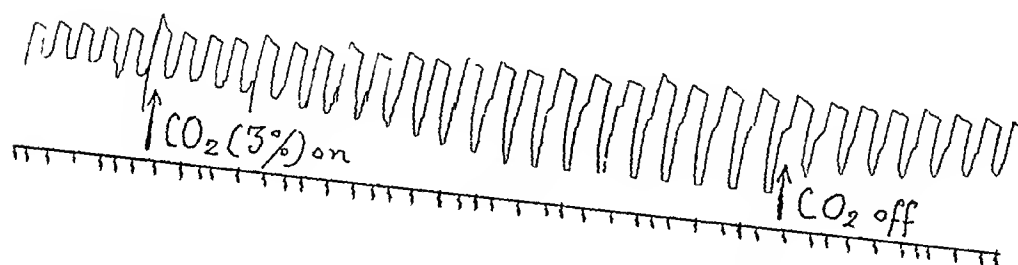
Ex- peri- ment	Period of Ex- peri- ment	Acetic Acid Infused		Gas Mixture Inhaled			Dura- tion of Experi- mental Period, Min	Blood Pressure			Comparison of Results
		Concen- tration, per Cent	Vol- ume, Cc	Carbon Dioxide, per Cent	Oxy- gen, per Cent	Nitro- gen, per Cent		Initial	Maxi- mum Attained	Devia- tion	
10	a			3	25	72	2	150	155	+ 5	$c \approx a + b + 10$
	b	n/20	2		Air		2	150	136	-14	
	c	n/20	2	3	25	72	2	140	150	+10	
17	a	n/20	3		Air		2	90	86	- 4	$c \approx a + b + 8$
	b			6	25	69	2	120	152	+32	
	c	n/20	3	6	25	69	2	114	150	+36	
18	a			3	25	72	2	120	121	+ 1	$c \approx a + b + 33$
	b	n/20	3		Air		2	90	86	- 4	
	c	n/20	3	3	25	72	2	90	120	+ 30	

centers To avoid an undesired rise of pressure within the cerebrospinal cavity, an amount of liquor was first allowed to escape through the puncture hole The amount of fluid injected that remained inside the dura is not exactly known because a part of it escaped after removal of the needle, it might be roughly estimated as about 0.5 cc of each of the fluids injected The control experiment (19, table 5) showed a slightly diminished effect of carbon dioxide after the injection of salt solution After the injection of the lactic acid, on the contrary, the effect of carbon dioxide was considerably intensified within a space of time, from one to twenty minutes after the injection (In experiment 20, the injection of the lactic acid itself caused a short-lasting fall of blood pressure of 16 mm, in the other experiments, short-lasting rises of 62, 13 and 57 mm, with a following return below the initial level The injection of salt solution did not alter the blood pressure)

Combination of Effect of Carbon Dioxide with Sodium Carbonate (table 7) —The results of these experiments are irregular concerning both the action of sodium carbonate itself and its influence on the effect

A_p (138)

6 min after inj of Lact acid (1%) into cerebrospinal cavity

A_p (110)

20 min after inj of lact acid (1%) into cerebrospinal cavity

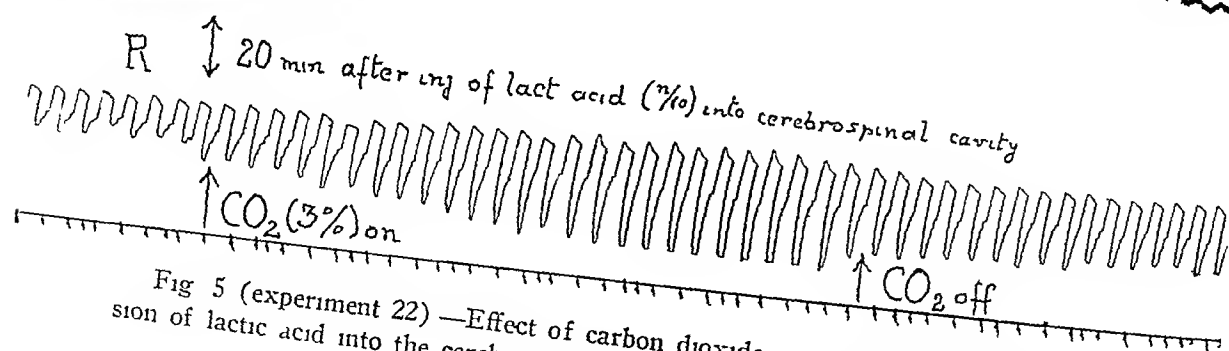


Fig 5 (experiment 22) —Effect of carbon dioxide increased through the infusion of lactic acid into the cerebrospinal cavity

TABLE 5—*Control with Saline Solution Injected into the Suboccipital Cavity and Effect of Carbon Dioxide*

Ex- peri- ment	Period of Ex- peri- ment	Sodium Chloride Injected		Onset of Inhalation of Carbon Dioxide, Minutes After Injection	Gas Mixture Inhaled			Dura- tion of Inhalation, Min	Blood Pressure			Com- parison of Results
		Concen- tration, per Cent	Vol- ume, Cc		Carbon Dioxide, per Cent	Oxy- gen, per Cent	Nitro- gen, per Cent		Ini- tial	Maxi- mum At- tained	Devia- tion	
19	a				3.6	25	71.4	2	74	95	+21	b = a-8
	b	0.9	cca 0.5	1	3.6	25	71.4	2	76	89	+13	

TABLE 6—*Effect of Carbon Dioxide After Injection of Lactic Acid into the Suboccipital Cavity*

Ex- peri- ment	Period of Ex- peri- ment	Lactic Acid Injected		Onset of Inhalation of Carbon Dioxide, Minutes After Injection	Gas Mixture Inhaled			Dura- tion of Inhalation, Min	Blood Pressure			Com- parison of Results
		Concen- tration, per Cent	Vol- ume, Cc		Carbon Dioxide, per Cent	Oxy- gen, per Cent	Nitro- gen, per Cent		Ini- tial	Maxi- mum At- tained	Devia- tion	
20	a				3.6	25	71.4	2	74	95	+21	c = a+9
	b	2	cca 0.5	3	3.6	25	71.4	2	68	98	+30	
21	a				3.6	25	71.4	2	120	140	+20	c = a+6
	b } c }	1	cca 0.5 {	5 20	3.6 3.6	25 25	71.4 71.4	2 2	107 102	133 138	+26 +36	
22	a				3.0	25	72.0	2	138	148	+10	c = a+20
	b } c }	1	cca 0.5 {	6 20	3.0 3.0	25 25	72.0 72.0	2 2	110 110	140 156	+30 +46	
23	a				3.6	25	71.4	2	120	145	+25	c = a+83
	b	5	cca 0.5	1	3.6	25	71.4	2	76	184	+108	

TABLE 7—*Sodium Carbonate Injected into the Central Stump of the Right Carotid and Effect of Carbon Dioxide*

Ex- peri- ment	Period of Ex- peri- ment	Sodium Carbo- nate Injected		Carbon Dioxide, per Cent	Gas Mixture Inhaled		Dura- tion of Experi- mental Period, Min	Blood Pressure			Comparison of Results
		Concen- tration, per Cent	Vol- ume, Cc		Oxy- gen, per Cent	Nitro- gen, per Cent		Initial	Maxi- mum Attained	Devia- tion	
24	a			6	25	69	2	134	164	+30	b = a+c+32 e = d+f+14 g = d+f+20
	b	n/10	3	6	25	69	2	116	190	+74	
	c	n/10	3		Air		2	118	130	+12	
	d			6	25	69	2	110	145	+35	
	e	n/10	3	6	25	69	2	110	165	+55	
	f	n/10	3		Air		2	90	96	+ 6	
	g	n/10	3	6	25	69	2	96	157	+61	
25	a			3	25	69	2	150	171	+21	b = a+c+5
	b	n/20	3	3	25	69	2	160	175	+15	
	c	n/20	3		Air		2	170	159	-11	
26	a			3	25	69	2	150	171	+21	b = a+c-4
	b	n/10	3	3	25	69	2	160	183	+23	
	c	n/10	3		Air		2	170	176	+ 6	
27	a	n/20	3		Air		2	110	105	- 5	b = a+c-37
	b	n/20	3	6	25	69	2	116	96	-20	
	c			6	25	69	2	90	112	+22	
28	a			6	25	69	2	66	146	+80	c = a+b-44
	b	n/20	3		Air		2	64	89	+25	
	c	n/20	3	6	25	69	2	66	127	+61	
29	a			6	25	69	2	66	146	+80	c = a+b-70
	b	n/10	3		Air		2	70	121	+51	
	c	n/10	3	6	25	69	2	70	131	+61	

of the carbon dioxide. The latter can be increased (experiments 24 and 25) or decreased (experiments 26, 28 and 29), or even transformed into an absolute fall of blood pressure (experiment 27)

Prolonged Increase of Blood Pressure by Continuous Perfusion of the Brain Stem with Lactic Acid—A cannula was tied into the right carotid and connected with a syringe the piston of which was pushed forward in a definite slow speed by a motor and pinion mechanism. All of these experiments were started after the blood pressure level had kept fairly constant for at least fifteen minutes. The readings of blood pressure were mostly done every two minutes. The results in experiment 30 were as follows

0-15 minutes	Average blood pressure 105 mm
15-70 minutes Lactic acid ($2\frac{1}{2}$ per cent, 0.15 cc per minute) into central stump of right carotid	Average blood pressure 126 mm
70-100 minutes	Average blood pressure, 144 mm
100-160 minutes Lactic acid (5 per cent, 0.15 cc per minute)	Average blood pressure 176 mm (Maximum, 222)

After the infusion of lactic acid was stopped, the blood pressure continued to increase to 242 mm (one hundred and seventy-second minute), and then fell gradually to 128 (two hundred and sixth minute). The animal was killed in the two hundred and thirtieth minute with a blood pressure of 132.

In both lactic acid periods the manometer cannula had to be washed out because of clotting. The manipulations on the artery were followed in both cases by a short rise and a considerable fall in blood pressure which was, however, compensated again within from fifteen to twenty minutes. The highest rise in blood pressure during infusion of lactic acid was 112 mm above the original level. The frequency and depth of respiration were not markedly increased during the whole experiment. The results of experiment 31 are shown in the following tabulation

0-15 minutes	Average blood pressure 133 mm
15-78 minutes Lactic acid (5 per cent, 0.15 cc per minute)	Average blood pressure 163 mm (Maximum 198)
78-84 minutes	Average blood pressure 162 mm

Another infusion of lactic acid was attempted but the animal collapsed and died within the first ten minutes. The highest rise during the

first lactic acid period amounted to $+64$ mm above the original level. The results in experiment 32 were as follows

0- 20 minutes		Average blood pressure 60 mm
20- 76 minutes	Lactic acid (5 per cent, 0.15 cc per minute)	Average blood pressure 85 mm (Maximum 98)
76- 82 minutes		Average blood pressure 103 mm
82-114 minutes	Lactic acid (5 per cent, 0.15 cc per minute)	Average blood pressure 105 mm (Maximum 120)

From the one hundred and fourteenth minute on, convulsions started and the blood pressure fell slowly, the animal was killed in the one hundred and twenty-fourth minute with a blood pressure of 60. The highest rises in the first lactic acid period were to $+38$ mm, in the second, $+60$ mm. The results in experiment 33 were as follows

0-15 minutes		Average blood pressure 124 mm
15-65 minutes	Lactic acid ($7\frac{1}{2}$ per cent, 0.15 cc per minute)	Average blood pressure 129 mm
65-75 minutes		Average blood pressure 129 mm
75-90 minutes	Lactic acid (15 per cent, 0.15 cc per minute)	Average blood pressure 195 mm (Maximum 260)

From the ninetieth minute on there occurred convulsions, rapid fall in blood pressure and death shortly thereafter. The highest rise during the second period was $+136$ mm, while the first period with a lactic acid concentration only half as strong had been practically ineffective. The results of experiment 34 are given in the following tabulation

0-15 minutes		Average blood pressure 141 mm
15-30 minutes	Lactic acid (5 per cent, 0.15 cc per minute)	Average blood pressure 175 mm (Maximum 188)

The highest rise was $+47$ mm. The results in experiment 35 were as follows

0-15 minutes		Average blood pressure 135 mm
15-45 minutes	Lactic acid (5 per cent, 0.15 cc per minute)	Average blood pressure 155 mm (Maximum 172)

After the fortieth minute convulsions occurred. The animal was killed at that time. The highest rise was $+37$ mm.

In these six experiments the blood pressure could be maintained on an artificially increased level during a period varying from a quarter of an hour to two hours through the infusion of lactic acid. The intensity of response was individually different.

Effect of Carbon Dioxide During Continuous Infusion of Lactic Acid (table 8) —The effect of carbon dioxide on the blood pressure is also increased during continuous infusion of lactic acid, starting from an elevated blood pressure level

TABLE 8—Continuous Infusion of Lactic Acid and Effect of Carbon Dioxide

Ex- peri- ment	Period of Ex- peri- ment	Lactic Acid Infused			Gas Mixture Inhaled			Dura- tion of Experi- mental Period, Min	Blood Pressure			Com- parison of Results
		Concen- tration, per Cent	Volume, Cc per Minute	Dura- tion, Min	Carbon Dioxide, per Cent	Oxy- gen, per Cent	Nitro- gen, per Cent		Ini- tial	Maxi- mum At- tained	Devia- tion	
36	a				3.5	25	71.5	2	106	122	+16	
	b	2.5	0.15	30	3.5	25	71.5	2	130	152	+22	b = a+6
	c	2.5	0.15	50	3.5	25	71.5	2	138	159	+21	c = a+5
	d	5.0	0.15	30	3.5	25	71.5	2	190	197	+7	d = a-9
37	a				3.5	25	71.5	2	128	159	+31	
	b	7.5	0.15	45	3.5	25	71.5	2	130	185	+55	b = a+24
38	a				3.5	25	71.5	2	124	148	+24	
	b	7.5	0.15	20	3.5	25	71.5	2	180	206	+26	b = a+2
39	a				3.5	25	71.5	2	130	162	+32	
	b	5.0	0.15	15	3.5	25	71.5	2	180	234	+54	b = a+22

TABLE 9—Hyperventilation Before and During Infusion of Lactic Acid

Ex- peri- ment	Period of Ex- peri- ment	Lactic Acid Infused			Standard Respiration per Minute		Hyperventilation				Average Blood Pressure			Deviation of Blood Pressure During Hyper- ventilation	
		Concentration, per Cent	Volume, Cc per Minute	Duration, Minutes	Number of Respirations	Stroke Volume	Respirations per Minute	Stroke Volume	Increase, per Cent	Duration, Minutes	Before Hyper- ventilation	During Hyper- ventilation	After Hyper- ventilation (Within Sec)	Average	Maximum
40	a				20	49	26	61	62	5	121	107	109 (50)	-14	-21
	b	5.0	0.07	30	20	49	26	61	62	5	159	128	148 (150)	-31	-39
41	a				20	49	26	61	62	5	60	60	73 (75)	± 0	-4
	b	5.0	0.07	10	20	49	26	61	62	5	105	93	99 (50)	-12	-21
42	a				20	55	26	67	58	5	113	104	104 (50)	-9	-15
	b	5.0	0.07	12	20	55	26	67	58	5	162	140	150 (130)	-22	-34
43	a				20	61	26	79	68	5	118	111	111 (75)	-7	-12
	b	7.5	0.15	10	20	61	26	79	68	5	147	122	131 (150)	-25	-41
	c	7.5	0.07	26	20	61	26	79	68	5	178	164	156 (100)	-14	-32
	d	7.5	0.07	45	20	61	26	79	68	5	183	173	173 (100)	-10	-18
44	a				26	55	26	69	26	5	110	130	149 (100)	+20	+38
	b				26	55	26	73	33	5	116	145	174 (40)	+29	+50
	c	5.0	0.15	6	26	55	26	69	26	5	130	130	139 (80)	± 0	-6, +10
	d	5.0	0.15	20	26	55	26	73	33	5	128	123	123 (60)	-5	-8, +2
45	a				26	55	26	73	33	5	60	99	119 (60)	+39	+52
	b	5.0	0.15	10	26	55	26	73	33	5	73	73	88 (60)	± 0	-8, +14

Effect of Hyperventilation Before and During Continuous Infusion of Lactic Acid (table 9) —These experiments were particularly difficult to do because of the irregularities in blood pressure caused by curare, which had to be used for maintaining a regular artificial respiration. Suitable constant conditions for periods of from eight to ten minutes as needed for this kind of experiment were only rarely available. Artificial hyperventilation was done in a very moderate degree for

excluding mechanical factors as far as possible. At each change of respiration rate the air pump had to be stopped for a few seconds, which usually caused a short-lasting slight asphyctic rise in blood pressure, but did not otherwise influence the conditions. The figures in

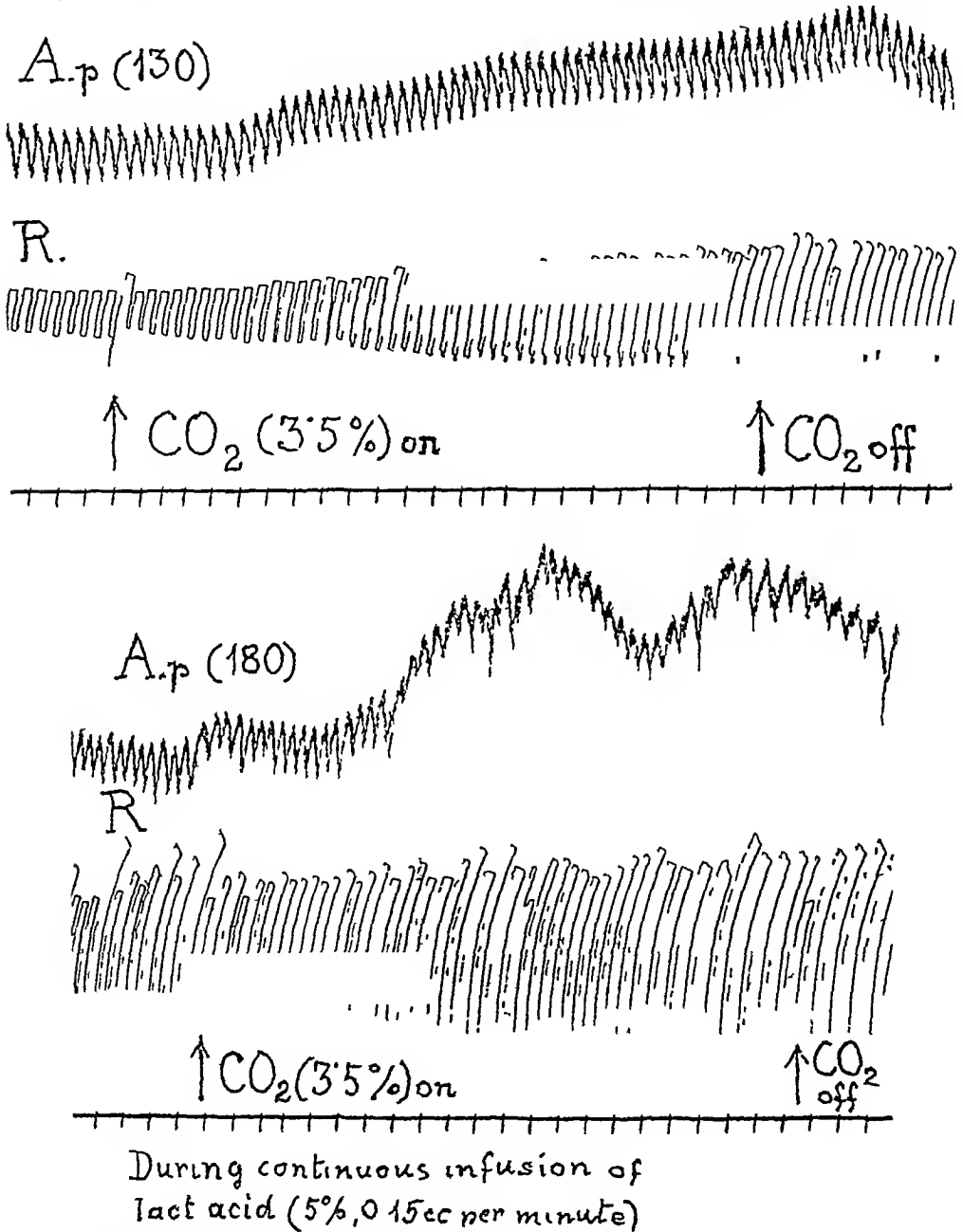


Fig 8 (experiment 39) —Effect of carbon dioxide increased through the infusion of lactic acid

table 9 are averages of blood pressure values measured on the diagrams at intervals of from twenty-five to thirty seconds. When definite waves in blood pressure occurred (experiment 40), only the tops of the waves were taken into consideration.

A.p (122)



R



$20 \times 49 \text{ cc}$ $\uparrow 26 \times 61 \text{ cc per' (= +62\%)} \longrightarrow$

$\uparrow 20 \times 49 \text{ cc}$
par'

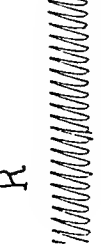


A.p (2160)

20



R



Infusion of lactic acid (5% 0.07 cc per') into center stump of right carotid for 30'

$20 \times 49 \text{ cc per'}$ $\uparrow 26 \times 61 \text{ cc per' (= +62\%)} \longrightarrow$

$\uparrow 20 \times 49 \text{ cc per}$

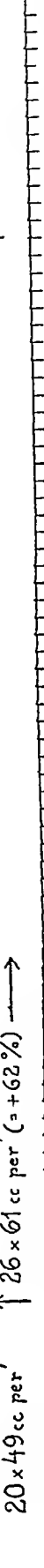


Fig 9 (experiment 40) —Effect of hyperventilation increased by the infusion of actic acid (The size of the respiratory movements appears different in the first and second part of the experiment on account of a change in position of the writing lever)

The hyperventilation caused a slight fall in blood pressure with the exception of one animal, in which it produced a marked rise. During the infusion of lactic acid, the falls of blood pressure were markedly increased, the rises were abolished.

TABLE 10—*Stimulation of the Cerebral Nerve Without and With Want of Oxygen**

Experiment	Period of Experiment	Gas Mixture Inhaled			Duration of Stimulus, Seconds	Blood Pressure				Comparison of Average Results
		Oxygen, per Cent	Nitrogen, per Cent	Duration, Seconds		Before Stimulus	During and After Stimulus	Increase	Average Increase	
46	a	6	94	60	5	40	44	4	4	$b = a + 3$
					5	40	44	4	4	
	b	6	94	60	5	45	54	9	7	
					5	43	48	5	5	
47	a	6	94	35	5	108	110	2	2	$b = a + 8$
	b				5	120	130	10	10	
48	a	10	90	20	5	124	170	46	46	$b = a + 26$
					5	116	161	45	45	
	b	10	90	20	5	130	213	83	72	
					5	152	214	62	62	

* The single stimuli were done at intervals of sixty seconds.

TABLE 11—*Stimulation of the Cerebral Nerve Without and With Infusion of Lactic Acid*

Experiment	Period of Experiment	Lactic Acid Infused		Duration of Stimulus, Seconds	Blood Pressure				Comparison of Average Results
		Concentration, per Cent	Volume, Cc per Minute		Before Stimulus	During and After Stimulus	Increase	Average Increase	
49	a	n/20	1	10	106	113	7	7	b = a+6
				10	107	112	5	5	
				10	107	116	9	9	
	b			10	100	115	15	13	
				10	99	110	11	11	
				10	98	111	13	13	
50	a	n/20	1	5	120	191	71	71	b = a+19
	b			5	116	206	90	90	
51	a	n/20	1	5	110	151	41	25	b = a+37
				5	104	122	18	18	
				5	98	114	16	16	
				5	123	203	80	62	
	b			5	115	176	61	61	
				5	116	178	62	62	
				5	109	167	56	56	
				5	125	176	51	51	

Sensitive Stimuli and Want of Oxygen (table 10)—The effect of peripheral sensitive stimuli on blood pressure is increased by a shortage of oxygen in the inhaled gas mixture.

Sensitive Stimuli and Infusion of Lactic Acid (table 11)—The increasing effect of peripheral stimuli on blood pressure is intensified during perfusion of the brain with lactic acid. In experiment 51, the evident parallelism of responses in blood pressure and respiration proves the central nervous character of the vasomotor response.

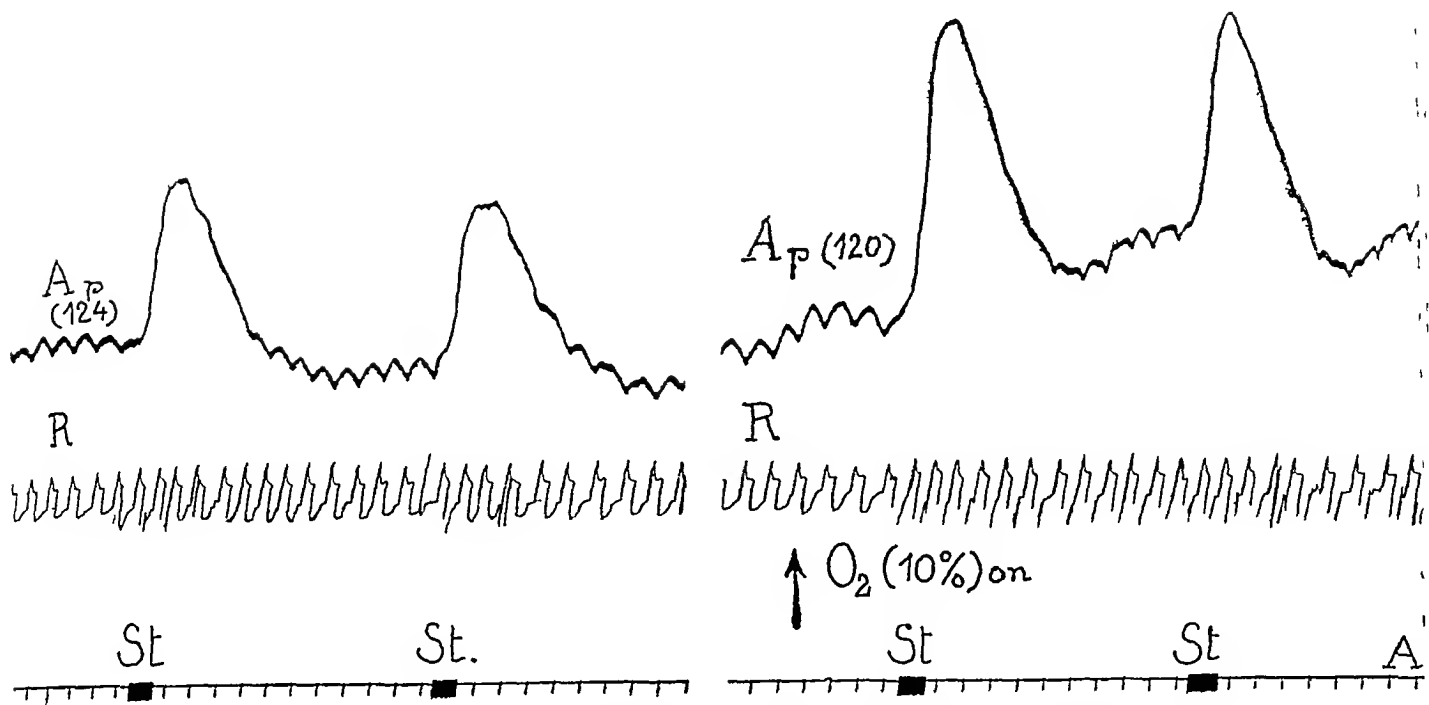


Fig 10 (experiment 48) —Effect of stimulation of the crural nerve increased by the want of oxygen

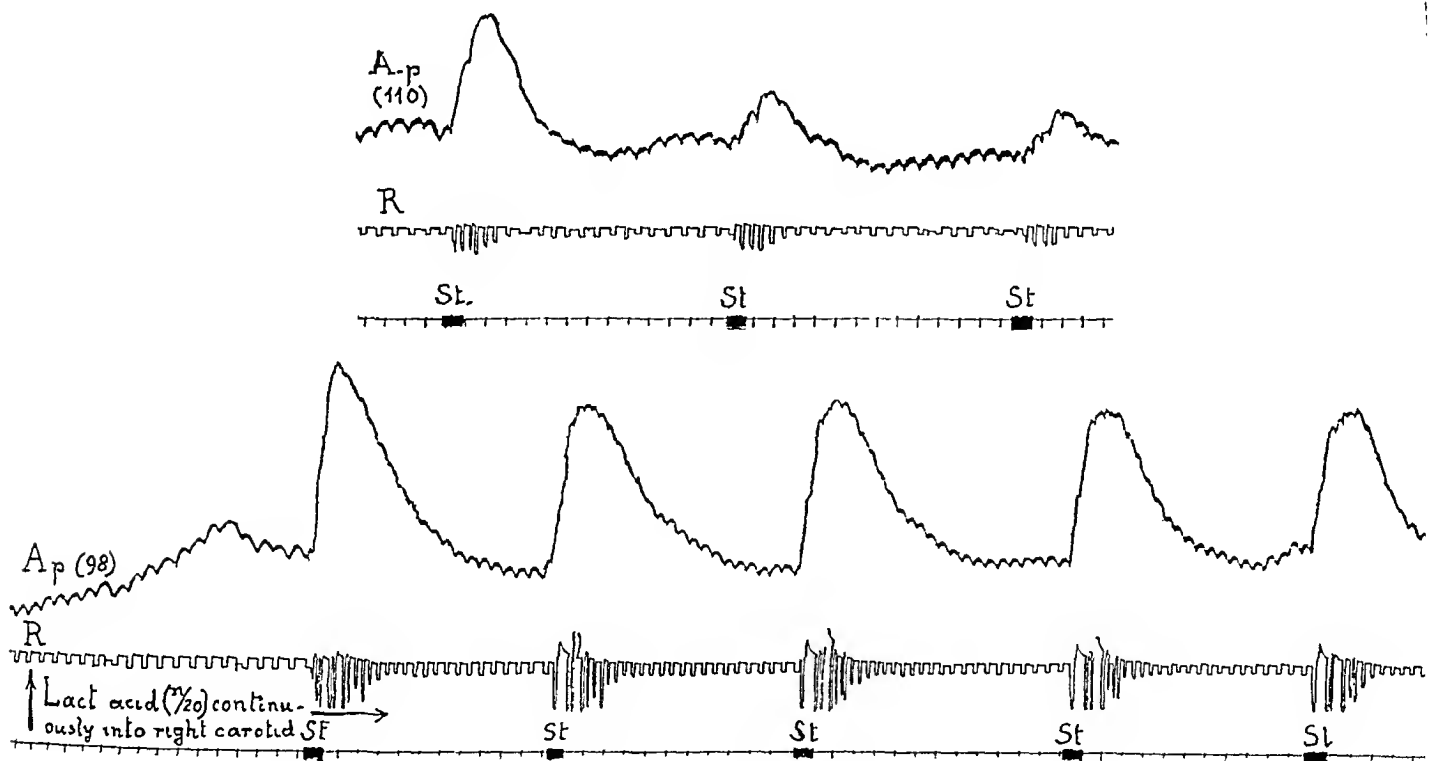


Fig 11 (experiment 51) —Effect of stimulation of the crural nerve increased by the infusion of lactic acid

Epinephrine and Want of Oxygen (table 12) —Want of oxygen was produced by complete shutting off of the respiratory air supply, which gives, of course, a combined effect of want of oxygen and accumulation of carbon dioxide, or by the administration of an oxygen-nitrogen mixture with a low oxygen concentration

TABLE 12—*Effect of Epinephrine Normally and During Want of Oxygen*

Ex- peri- ment	Period of Ex- peri- ment	Epinephrine Injected		Gas Mixture Inhaled		Blood Pressure			Comparison of Results
		Amount, Mg	Place	Oxy- gen, per Cent	Nitro- gen, per Cent	Initial	Maxi- mum Attained	Devia- tion	
52	a	0.012	Right carotid	Air		60	116	+56	b = a-78
	b			0	0	66	172		
		0.012	Right carotid	0	0	172	150	-22	
53	a	0.015	Right carotid	Air		60	94	+34	b = a-62
	b			0	0	60	144		
		0.015	Right carotid	0	0	144	116	-28	
54	a	0.006	Femoral vein	Air		108	164	+56	b = a-72
	b			10	90	60	150		
		0.006	Femoral vein	10	90	150	134	-16	
55	a	0.006	Femoral vein	Air		116	146	+30	b = a-38
	b			5	95	90	136		
		0.006	Femoral vein	5	95	134	126	-8	
56	a	0.012	Femoral vein	Air		90	114	+24	b = a-28
	b			5	95	90	128		
		0.012	Femoral vein	5	95	128	154	+26	

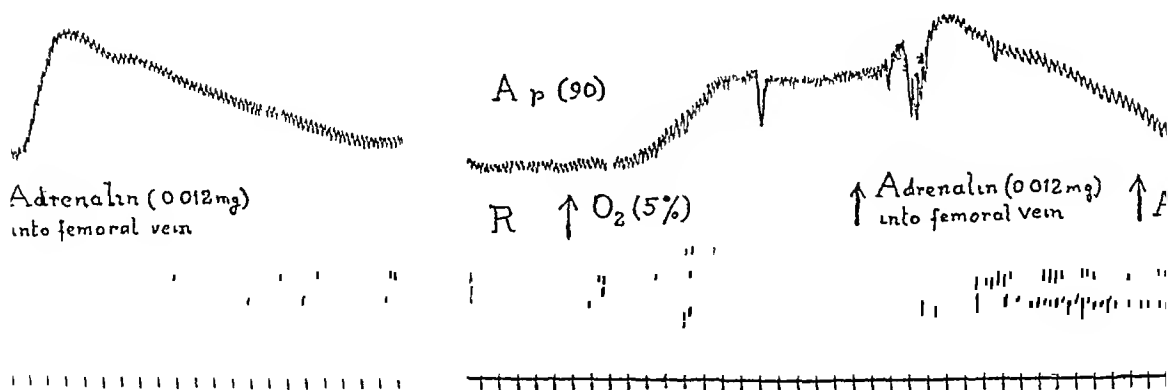


Fig 12 (experiment 56) —Effect of epinephrine altered by the want of oxygen

In four of five experiments, the increasing effect of epinephrine on the blood pressure was inverted into a fall during want of oxygen, in one experiment (56), it was diminished by 50 per cent

Epinephrine and Infusion of Lactic Acid (table 13) —In contrast to the conditions during the shortage of oxygen, the effect of epinephrine on the blood pressure is only insignificantly altered during perfusion of the brain with lactic acid

TABLE 13—Effect of Epinephrine Normally and During Infusion of Lactic Acid

Ex- peri- ment	Period of Ex- peri- ment	Lactic Acid Infused			Epinephrine Injected		Blood Pressure			Com- parison of Results
		Concen- tration, per Cent	Volume, Cc per Minute	Dura- tion, Min	Amount, Mg	Place	Initial	Maxi- mum At- tained	Devia- tion	
57	a				0.006	Femoral vein	112	132	+20	b = a+2
	b	7.5	0.07	30	0.006	Femoral vein	148	170	+22	
58	a				0.012	Femoral vein	114	164	+50	b = a-5
	b	7.5	0.07	20	0.012	Femoral vein	140	185	+45	
59	a				0.012	Femoral vein	102	160	+58	b = a-16
	b	5.0	0.15	5	0.012	Femoral vein	138	180	+42	
60	a				0.012	Femoral vein	130	182	+52	b = a-2
	b	7.5	0.15	10	0.012	Femoral vein	164	214	+50	

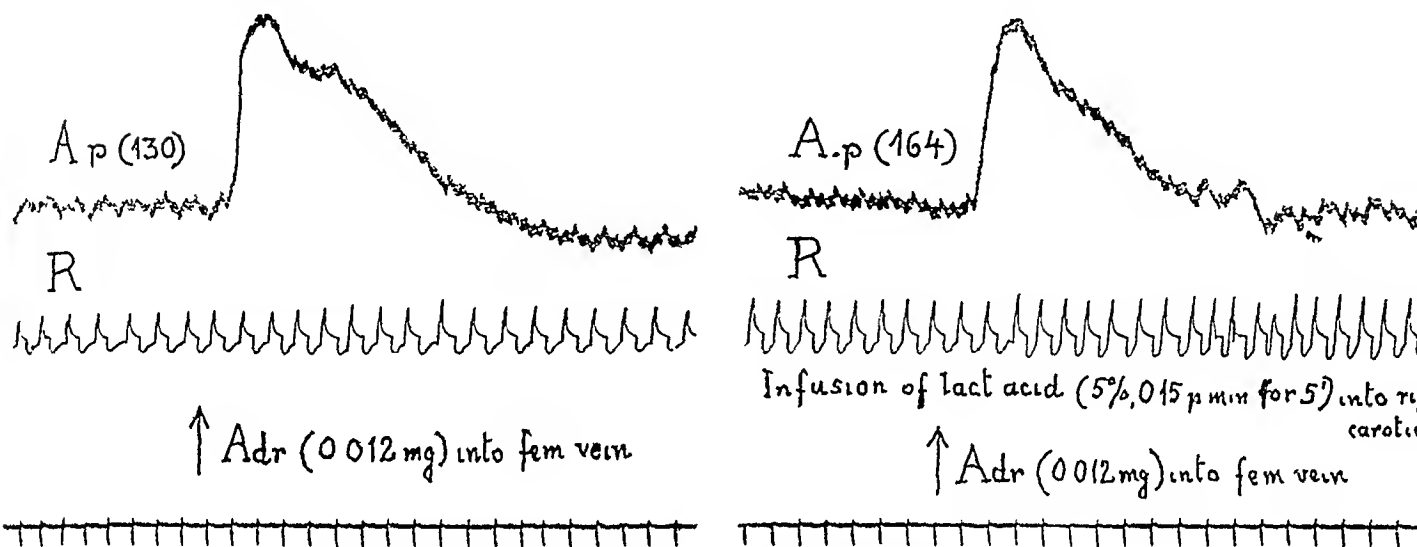


Fig 13 (experiment 60) —Effect of epinephrine unaltered by the infusion of lactic acid

COMMENT

The experiments described show a striking accordance of characteristic symptoms in clinical essential hypertension and in the experimental conditions that were intended to imitate the assumed pathogenic causes of essential hypertension, namely, need of oxygen and the presence of an increased amount of lactic acid within the cerebral vasomotor center region. In my experiments there was used a cutting down of the oxygen supply to the whole body. Hence also the peripheral circulatory apparatus was exposed to this abnormal condition at the same time. It has been stated by various authors (Mathison,²⁰ Romanese,⁶⁷ McGinty and Gesell,²⁶ Gollwitzer-Meier⁶⁸ and others) that general anoxemia in consequence of the diminished inhalation of oxygen leads to an increase of the arterial blood pressure. Gollwitzer-Meier,⁶⁸ who used for her experiments concentrations of oxygen within about the same range as I (from 14 to 6 per cent), observed a slight increase of the

⁶⁷ Romanese, R. Boll. d. Soc. ital. di biol. sper. **2** 887, 1928

⁶⁸ Gollwitzer-Meier, K. Arch. f. d. ges. Physiol. **220** 434, 1928

time volume of the heart, to which she attributed, however, less importance for this increase of blood pressure than to an irritation of the vasomotor centers, an opinion which has also been expressed by Mathison,²⁰ A. Loewy¹³ and others. Dale and Richards⁶⁹ have given evidence for it by tying up both carotids and one vertebral artery, Gurdjian²² demonstrated it by the effect of the local application of sodium cyanide on the brain stem in the vasomotor region, which prevents oxidation and causes a strong rise of blood pressure. The action of shortage of oxygen on the tonus of the vasomotor centers seems, however, not to be direct but due to the formation and accumulation of acid substances, especially of lactic acid as has been shown similarly for the respiratory center by Haldane and his collaborators,⁵⁰ Winterstein⁷⁰ and Gesell.³³ Besides, there occurs during general anoxemia, of course, a formation of lactic acid in the other parts of the body (Araki,⁷¹ Ryffel⁷² and others) which will reach the brain by the blood stream. With regard to the prevailing central effect of anoxemia on blood pressure, it is justifiable to consider the effect on the blood pressure of breathing low concentrations of oxygen as practically analogous to that of a diminished local oxygen supply to the vasomotor centers.

The injection of acids into the central stump of the right carotid artery, as done by Mathison²⁰ and Gollwitzer-Meier,³⁴ is a suitable way to let these substances act on the brain tissue, although they are, of course, also distributed to a certain extent in the peripheral vascular system. The latter fact, however, is not of great practical importance. It is true that acids exert a certain dilating action on the peripheral vessels (Fleisch⁷³ and others), but at the same time their stimulating influence on the vasoconstrictory centers is so strong that it overcomes the dilatation entirely and leads to a considerable rise of blood pressure (Cobet,¹⁴ Ganter⁷⁴). Thus the results of my experiments with injection into the carotid artery are to be considered as essentially due to perfusion of the brain stem.

A long-lasting shortage of oxygen in the inhaled air is not apt to produce an equally long-lasting rise in blood pressure, because of the weakening of the heart, while it is possible to maintain the blood pressure on an abnormally high level during hours by prolonged infusion of lactic acid (experiments 30 to 35).

69 Dale, H. H., and Richards, A. N. *J. Physiol.* **63** 201, 1927.

70 Winterstein, in Bethe, A., von Bergmann, G., Embden, G., and Ellinger, A. *Handbuch der normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1929, vol. 9, p. 515.

71 Araki. *Ztschr. f. physiol. Chem.* **15** 335 and 546, 1891, **19** 422, 1894.

72 Ryffel. *J. Physiol.*, vol. 39, *Proc. Physiol. Soc.*, p. xxix, 1909-1910.

73 Fleisch. *Arch. f. d. ges. Physiol.* **171** 86, 1918.

74 Ganter, G. *Arch. f. exper. Path. u. Pharmacol.* **138** 276, 1928.

The purpose of my experiments, however, was not to state the mere stimulating action of the need of oxygen and of lactic acid, which is well enough known, but to investigate the influence of these factors on the irritability of the vasomotor centers. The latter could be shown to be markedly increased as far as the reaction to increased carbon dioxide in the blood (inhalation of carbon dioxide), to decreased carbon dioxide in the blood (hyperventilation) and to peripheral sensitive stimuli (from the crural nerve) is concerned.

The experiments with inhalation of carbon dioxide (experiments 1 to 15, 19 to 23, 36 to 39) showed a considerably stronger rise of blood pressure if combined with a diminished supply of oxygen or with the infusion of lactic acid (the latter both in short and in prolonged periods), or with the injection of lactic acid into the suboccipital cavity. The rise in blood pressure not only consisted in a mere summation of the effect of anoxemia or lactic acid on one side and the effect of carbon dioxide on the other, but it was almost without exception greater than the mathematical sum of both. The figures found, of course, cannot be considered as an absolute quantitative expression of the dynamic processes in the vascular system, but the fact of a mutual increase of efficiency is evident, especially in such experiments in which one or both factors (oxygen need and lactic acid, respectively), alone did not or almost did not raise the blood pressure but still gave a stronger rise with carbon dioxide than carbon dioxide alone (experiments 4, 10, 12 and 37). This is also the case in the experiments with the injection of lactic acid into the cerebrospinal cavity, which itself produced a rise of blood pressure lasting only a short time, with an early return to or even below the normal level, while it caused a markedly increased effect of the inhalation of carbon dioxide within twenty minutes (experiments 20 to 23). Hence the presence of lactic acid in the center region can be sufficient to intensify the effect of the stimulus of carbon dioxide even if it is too weak to produce any direct effect by itself. The increasing influence of lactic acid on the effect of carbon dioxide was missed only in a state of exceedingly strong excitation of the centers by the infusion of lactic acid and on a very high level of blood pressure (experiment 36).

A few experiments have also been made with acetic acid. It acts in the same way as lactic acid as far as the intensification of the effect of carbon dioxide is concerned, although its own effect on the blood pressure in the concentrations used was rather a slightly depressant one (experiments 16 and 18). The effects of alkali (sodium carbonate) were irregular (experiments 24 to 29). Gesell³³ and Gollwitzer-Meier³⁴ found a decreasing influence of sodium carbonate injected intravenously

on both blood pressure and respiration. This is not regularly the case with injections into the carotid, on the contrary a considerable rise of blood pressure was sometimes noticed (+25 and +51 mm, experiments 28 and 29). The influence of sodium carbonate on the effects of carbon dioxide was not uniform, and varied within a wide range between strong increases and decreases. A possible explanation for this behavior might be seen in the statement of Jacobs⁷⁵ that even alkaline substances can lead to an acid reaction in the interior of the cells which they surround. For instance, bicarbonate buffer mixtures let the bicarbonate radical pass through the cell membrane, and as a matter of fact Gesell³³ found that the intravenous injection of sodium bicarbonate, although itself alkaline, increases the hydrogen ion concentration of the cerebrospinal fluid and acts like an acid on the respiratory center. Gollwitzer-Meier³⁴ observed the same concerning the effect of bicarbonate on the blood pressure. One can assume, therefore, that a combination of sodium carbonate with buffers of the blood, with the normal amount of carbon dioxide present, and especially with increased amounts of carbon dioxide during the inhalation of carbon dioxide, might form sodium bicarbonate and so lead to the paradoxical acid-like effect in varying degrees which probably mainly depend on the mutual relations in concentration ($\text{Na}_2\text{CO}_3 + \text{CO}_2 + \text{H}_2\text{O} = 2\text{NaHCO}_3$).

Hyperventilation causes a loss of carbon dioxide and usually a more or less marked fall of blood pressure, which has been attributed partly to mechanical changes in the circulation (Vincent and Cameron,⁷⁶ Janeway and Ewing,⁷⁷ Hill and Flack,⁷⁸ Vincent and Thompson,⁷⁹ Rappaport³¹) and partly to the diminished stimulus of carbon dioxide on the vasomotor centers (Henderson,⁸⁰ Dale and Evans,⁸¹ Hill and Flack,⁷⁸ Vincent and Thompson⁷⁹). Dale and Evans⁸¹ in accordance with Henderson's conception, considered the content of the blood in undissociated carbon dioxide as essentially important for the tone of the vasomotor centers. Stross⁸² did not find, however, a moderate loss of carbon dioxide of considerable influence on the blood pressure. In my experiments (40 to 45) which have been done in curarized decerebrate animals with artificial respiration, the artificial increase of respiration amounted only to from 26 to 68 per cent. With the exception

75 Jacobs, M. H. *Am J Physiol* **58** 457 1920-1921

76 Vincent and Cameron. *Quart J Exper Physiol* **9** 64, 1915

77 Janeway and Ewing. *Am J Surg* **59** 160 1914

78 Hill and Flack. *J Physiol* **40** 354, 1910

79 Vincent, S., and Thompson, J. H. *J Physiol* **66** 307 1928

80 Henderson, Y. *Am J Physiol* **21** 126, 1908

81 Dale, H. H., and Evans, C. L. *J Physiol* **56** 125 1922

82 Stross, W. *Arch f exper Path u Pharmacol* **131** 18 1928

of one animal in which each period of hyperventilation produced a considerable rise of blood pressure for unknown reasons, there was a slight drop of blood pressure during increased respiration. During the infusion of lactic acid into the right carotid artery, this hyperventilatory fall was markedly deeper, and the exceptional rises of blood pressure (in the animal mentioned) were checked if hyperventilation was done during the infusion of lactic acid. Hence the latter causes, both absolutely and relatively, a stronger decreasing effect of hyperventilation on the blood pressure than it appears to do under normal conditions.

In summarizing all the experiments discussed, one can conclude that the sensitivity of the vasomotor centers to changes in the carbon dioxide content of the blood (both to increase and to decrease of carbon dioxide) is considerably strengthened by the presence of lactic acid in the region of the vasomotor center and as a consequence of local want of oxygen.

This increased sensitivity, however, is not only evidenced in chemically stimulating tests as carbon dioxide but also in purely nervous stimuli from the periphery. Faradic stimulations of the crural nerve (central stump) caused considerably higher rises in blood pressure when they were combined with inhalation of a low percentage of oxygen or with infusion of lactic acid (experiments 46 to 51).

Experiments that were done for comparing the action of epinephrine on the blood pressure under normal conditions and under the influence of lactic acid and want of oxygen showed that the ordinary rising effect was inverted or at least considerably weakened during the shortage of oxygen, while it was very little altered during artificial hypertension produced through the infusion of lactic acid. To understand this peculiar behavior one has to consider the action of epinephrine on the circulation of the brain. The literature on this topic is fairly contradictory. Some authors claim an almost complete lack of innervation of the vessels of the brain and a passive dilatation of these vessels as a consequence of a rise in the systemic blood pressure through epinephrine (Schneider⁸³ and others). In recent work Forbes and Wolff⁸⁴ showed, however, that this is not entirely true, at least as far as the vessels on the surface of the brain are concerned. These vessels contract under the direct local influence of epinephrine, while they become dilated if their com-

83 Schneider, E. C. *Am J Physiol* **84** 202, 1928.

84 Forbes, H. S., and Wolff, H. G. *Cerebral Circulation. III. The Vasomotor Control of Cerebral Vessels*, *Arch Neurol & Psychiat* **19** 1057 (June) 1928.

paratively weak contracting power is overcome by a stronger rise in systemic pressure. Dale and Richards⁶⁹ stated that doses of epinephrine that increase the blood pressure under normal conditions produce a fall of pressure if the blood supply to the brain is cut down by tying up the carotids and one vertebral artery and if the vasomotor centers are thus irritated. They attributed this phenomenon to an improvement of the poor circulation in the brain through the action of epinephrine. The results of my experiments can hardly be more easily explained than by the same assumption of an increased flow of blood through the brain—at least through the brain stem—under the influence of epinephrine.

(a) The diminution of oxygen in the inspiratory air leads to the accumulation of lactic acid in the centers and increased blood pressure. If epinephrine increases the circulation through the centers, the lactic acid will be removed, and the blood pressure will fall toward the normal.

(b) If lactic acid is perfused through the region of the vasomotor center by adding it to the arterial blood, and if the blood pressure is thus increased, an increased perfusion of the brain will, of course, not diminish the lactic acid within the center region, no considerable alteration of the pressure-raising effect of epinephrine will take place.

COMPARISON WITH CLINICAL CONDITIONS

As mentioned, the main purpose of my experiments has been the experimental imitation of characteristic symptoms of clinical hypertension. These characteristic clinical symptoms are as follows: (1) elevated blood pressure, (2) hypersensitivity of the vasomotor centers to changes in the carbon dioxide content of the blood by the inhalation or exhalation of carbon dioxide, (3) hypersensitivity of the centers to peripheral nervous stimuli and (4) reversion or weakening of the effect of epinephrine on the blood pressure.

There was, of course, no possibility of producing an elevation of blood pressure for a period to be compared with the clinical hypertension that is often maintained during years. Still the fact that a considerable increase of blood pressure could be produced for as long as two hours by prolonged infusion of lactic acid proves that a chemical stimulus of this kind does not cause only short-lasting effects with rapidly following fatigue of the stimulated centers. The assumption of a local stimulating chemical factor in the region of the vasomotor center of hypertonic persons, therefore, seems to be justified from the beginning.

The hypersensitivity to the inhalation of carbon dioxide that could be clearly demonstrated in the experiments under the conditions which cause the presence of abnormal amounts of lactic acid in the vasomotor

It is probable also that the increased response of blood pressure to psychic emotions in hypertonic patients might occur on the same basis—reflex transmission of central nervous excitements to the hypersensitive vasomotor centers

The peculiarities of the effect of epinephrine on hypertonic persons and its frequent weakness or paradoxical inversion can possibly be explained as due to a removal of accumulated lactic acid from the vasomotor center through the improvement of the blood flow through this region under the influence of epinephrine. This explanation would not be incompatible with Kylin's⁶¹ conception of a general change in the tonus of the vasomotor nervous system as the basis of the paradoxical effect of epinephrine on hypertonic persons

My experimental results show that the vasomotor center reacts in about the same way that Haldane,⁵⁰ Winterstein,⁷⁰ Gesell,³³ Straub³⁶ and others have shown that the respiratory center does. The clinical syndrome of "cerebral dyspnea" has been described by Straub³⁶ and von Romberg³⁷. It has been conceived as due to local disturbances of the circulation of the respiratory center. Von Romberg emphasized the frequency of this feature in cases of hypertension, which appears natural if one assumes the same pathogenic factors to be responsible also for the development of hypertension, as is suggested by my experiments. It is rather surprising that the parallelism of hypertension and "cerebral dyspnea" is not more regular. A satisfactory explanation for this discrepancy, which as a matter of fact is almost more frequently observed than the simultaneous occurrence of both features, cannot be given at present. There are, however, possible explanations, as, for instance, a (although improbable) local separation of the vasomotor centers and the respiratory centers which would be considerable enough to allow the development of vascular troubles in only one of them, the other remaining unaffected, or a generally lower irritability of the respiratory center, which is suggested by some of my experiments in which the effects on blood pressure appear markedly stronger than those on respiration.

A summary of the conception of the origin of hypertension as it is suggested by my experiments could be formulated as follows. A primary disturbance of the blood flow through the region of the vasomotor center (or temporarily by vessel spasms or continuously by sclerotic alterations of the vessels of this region) leads to a diminished supply of oxygen and the subsequent formation and accumulation of abnormal amounts of lactic acid within the nerve cells of the centers. In the first stages the presence of lactic acid produces only an increased irritability of the centers—the pressure is not yet constantly high, but rises abnormally easily and strongly. Little by little the alteration of the center vessels and consequently the accumulation of lactic acid

develop enough to produce a constant irritation of the centers. The pressure level rises. At the same time the hyperirritability persists, and all kinds of stimuli—sensitive sensations, psychic emotions, muscular activity and even the normal carbon dioxide content of the blood—contribute to the increase of blood pressure and its lability. If a certain upper limit is attained, the hyperirritability can become less marked again because of the prevailing effect of the strong irritation through lactic acid in comparison to which the other stimuli lose in efficiency—"fixed hypertension." Factors that temporarily improve the blood flow through the centers might cause a fall in blood pressure (for instance, epinephrine or, as I have found in the majority of hypertonic persons, diathermy of the brain stem).

The question of the causal connection between hypertension and general arteriosclerosis cannot be discussed here. It may be mentioned that in some cases there could be a primary localized sclerosis within the brain stem (isolated arteriosclerosis of the brain is not a rare occurrence) with subsequent hypertension that would lead to a more generalized arteriosclerosis, kidney conditions, etc., and as a vicious circle to further deterioration in the region of the vasomotor centers. The essential primary factors of the whole process, however, are unknown. Kylin's⁶¹ investigations concerning the ion balance and its influence on the vegetative nervous system seem to show a promising way of discovering the origin of pathologic conditions of the vessels of the nerves. On the other hand, the anatomic observations of Bordley and Baker¹⁷ and others concerning sclerosis of the vessels of the vasomotor centers in hypertension and the large amounts of lactic acid found in brain tissue after shortage of oxygen by McGinty and Gesell,²⁶ Haldi, Ward and Woo²⁸ and Cobet²⁷ can be considered as a basis for the validity of the conception mentioned.

SUMMARY

In decerebrate cats with the vagi cut, the following experimental results were obtained

- 1 There was a strong increase of the arterial blood pressure for a period up to two hours by the continuous perfusion of the brain stem with blood containing abnormally high amounts of lactic acid.

- 2 Hyperirritability of the vasomotor centers resulted under the influence of a shortage of oxygen or perfusion with lactic acid, or with the injection of lactic acid into the suboccipital cavity. The inhalation of carbon dioxide causes a considerably greater rise and the hyperventilation (loss of carbon dioxide) a greater fall in blood pressure under these conditions than occur under normal conditions.

3 Sensitive stimuli cause higher rises of blood pressure during the conditions mentioned than they do normally

4 The effect of epinephrine is considerably weakened and inverted during the lack of oxygen, it is scarcely altered during perfusion with lactic acid

5 Acetic acid increases the irritability of the vasomotor center in the same way as lactic acid, alkali (sodium carbonate) gives irregular effects

6 These experimental results correspond to the following characteristic features of essential hypertension (1) high blood pressure, (2) hypersensitivity to the inhalation of carbon dioxide (abnormal increase of blood pressure) and to hyperventilation (abnormal fall of blood pressure), (3) hypersensitivity to peripheral sensitive stimuli and (4) weakened or inverted effect of epinephrine

7 The conclusion was reached that the symptoms of "essential" (not nephritic) hypertension can be considered due to the local need of oxygen and the accumulation of lactic acid within the vasomotor centers of the brain stem as a consequence of local circulatory disturbances (spasms, sclerosis) The actual level of the blood pressure in hypertension would accordingly be composed of the sum of the stimulus through lactic acid plus the pathologically increased responses to the stimulus of the normal carbon dioxide tension of the blood and of different kinds of sensitive and emotional stimuli

SERUM AND PLASMA BILIRUBIN

A COMPARATIVE QUANTITATIVE STUDY OF ONE HUNDRED CASES *

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The van den Bergh reaction¹ for bile pigment in the blood was introduced in 1918. As originally proposed, the determinations were made with the blood serum. During the twelve years that have elapsed, the test has received general and widespread acceptance. Today, both in the original technique and in the modifications, most important of which is the Thannhauser and Andersen method,² serum is still employed.

McNee and Keefer³ were the first to suggest the use of plasma instead of serum. These workers applied the original van den Bergh technique to the plasma obtained from oxalated blood in the proportion of 0.2 cc of 10 per cent potassium oxalate to from 10 to 15 cc of whole blood. The results led them to assert that plasma and serum may be utilized equally well.

Shay and Schloss⁴ disagreed with these observers. In a series of eleven simultaneous examinations of serum and plasma by the original van den Berg and the Thannhauser and Andersen methods, they found an agreement of the readings for the serum and plasma in only four instances. In fourteen instances, the reading for the serum were greater by amounts ranging from 0.1 to 7.5 units; in three instances, the readings for the plasma were of greater magnitude, of the order of 0.1 to 0.4 unit.

In view of these diametrically opposed opinions, and because the original suggestion was not accompanied by tables to illustrate the

* Submitted for publication, Sept. 15, 1930.

¹ From the Pathological Laboratories of the Brownsville and East New York Hospital, Brooklyn.

1 van den Bergh, H. *Der Gallenfarbstoffe im Blute*, Leiden, S. C. van Doesburgh, 1918.

2 Thannhauser, S. J., and Andersen, E. *Methodik der quantitativen Bilirubinbestimmung in menschlichen Serums*, *Deutsches Arch. f. klin. Med.* **137**: 179 (Aug.) 1921.

3 McNee, J. W., and Keefer, C. S. *Clinical Value of van den Bergh Reaction for Bilirubin in Blood, with Notes on Improvements in Its Technique*, *Brit. M. J.* **2**: 52 (July 11) 1925.

4 Shay, H., and Schloss, E. M. *van den Bergh Reaction: Comparison of Techniques*, *J. Lab. & Clin. Med.* **15**: 292, 1929.

found in the group with coupling of equal duration. In fact, the largest difference in readings observed in the entire series, 0.8 unit, occurred in the group with equitemporal coupling (specimen 20).

An analysis of our figures (table 3) shows exact agreement in 70 per cent of our specimens. In the 30 per cent in which the readings did not agree, an approximately equal number of specimens showed

TABLE 2—*Simultaneous Determinations of the Bilirubin of One Hundred Unselected and Consecutive Serums and Plasmas*

Specimen Number	Plasma Reading, Units	Serum Reading, Units	Specimen Number	Plasma Reading, Units	Serum Reading, Units
1	0.3	0.3	51	0.2	0.2
2	0.2	0.2	52	No reaction	No reaction
3	0.6	0.6	53	1.2	1.2
4	0.1	0.4	54	3.1	3.2
5	0.5	0.4	55	0.2	0.2
6	No reaction	No reaction	56	1.1	1.0
7	6.2	6.2	57	0.3	0.3
8	4.9	5.0	58	0.2	0.2
9	1.3	1.2	59	1.8	2.0
10	1.0	1.1	60	0.5	0.5
11	1.0	1.0	61	1.5	1.5
12	0.3	0.3	62	0.1	0.2
13	0.4	0.3	63	0.2	0.2
14	5.5	5.6	64	0.2	0.2
15	7.5	7.5	65	0.1	0.1
16	8.3	8.2	66	0.1	0.1
17	10.0	10.4	67	5.3	5.2
18	2.4	2.4	68	12.0	11.8
19	0.6	0.6	69	0.5	0.5
20	16.0	16.8	70	0.2	0.2
21	7.0	6.8	71	2.0	2.1
22	0.3	0.3	72	0.2	0.2
23	0.3	0.2	73	0.6	0.6
24	0.3	0.2	74	0.8	0.8
25	0.2	0.2	75	0.9	0.8
26	0.5	0.5	76	2.8	2.9
27	No reaction	No reaction	77	0.3	0.3
28	No reaction	No reaction	78	1.4	1.3
29	0.6	0.6	79	0.2	0.2
30	0.4	0.5	80	0.1	0.1
31	0.2	0.2	81	0.3	0.3
32	0.1	0.1	82	0.4	0.3
33	0.2	0.2	83	0.3	0.3
34	1.1	1.1	84	0.5	0.5
35	No reaction	No reaction	85	0.4	0.4
36	1.4	1.5	86	0.2	0.2
37	6.2	6.2	87	0.6	0.6
38	No reaction	No reaction	88	6.2	6.2
39	1.1	1.1	89	0.4	0.3
40	2.7	2.5	90	5.0	5.1
41	1.0	1.0	91	0.3	0.4
42	10.0	10.0	92	0.2	0.2
43	No reaction	No reaction	93	0.5	0.5
44	2.5	2.4	94	0.3	0.3
45	0.2	0.3	95	4.1	4.1
46	0.2	0.2	96	9.5	9.5
47	0.1	0.1	97	16.0	16.0
48	0.8	1.0	98	0.3	0.3
49	0.4	0.4	99	6.2	6.2
50	0.5	0.5	100	0.1	0.1

higher readings for the serum (in 16 per cent) and higher readings for the plasma (in 1.4 per cent), a division further borne out when the readings were grouped according to their magnitude. Thus in the group of readings between 0.6 and 1 unit, 66 per cent agreed exactly (eight of twelve readings), of the remaining 33 per cent (four of twelve), the reading for the serum was greater than that for the plasma

figures on which the opinion was based while the dissenting opinion was based on so few determinations, we decided to reinvestigate the subject. If plasma could be substituted for serum, it would mean a considerable saving of time for the laboratory, the performance of the reaction would be facilitated as it could then be carried out with oxalated blood taken in the course of routine chemical examinations, and additional inconvenience to the patients incident to an added venipuncture would be avoided. To this end, we performed simultaneous determinations quantitatively on 100 consecutive and unselected serums and plasmas from cases in the hospital and from the dispensary. The Thannhauser and Andersen modification was used in all instances, since with that

TABLE 1—*Differences Between Simultaneous Readings for the Serum and the Plasma Calculated from Table 3 of Shay and Schloss*

	van den Bergh Technic	Thannhauser and Andersen Technic
Readings agreeing	4	0
Readings disagreeing	7	11
Serum readings greater (units)	6	8
0.1	1	0
0.2	0	1
0.4	0	1
1.2	1	0
1.3	2	0
1.4	0	1
1.7	0	1
3.0	0	1
4.1	1	0
4.2	1	0
4.3	1	0
5.4	0	1
7.4	0	1
7.5	0	1
Plasma readings greater (units)	1	2
0.1	1	0
0.2	0	1
0.4	0	1

method all the azobilirubin could be retained for estimation in the supernatant fluid, and because the discrepancies noted by Shay and Schloss were both more frequent and of greater magnitude. Muller's cobalt sulphate standard⁵ was used throughout.

Table 2 shows a remarkable agreement of the readings for both the serum and the plasma. In each of the first fifty determinations, coupling was allowed to take place for one-half hour before the proteins were precipitated. In the latter half of the series (specimens 50 to 75) coupling of the diazo reagent and serum was allowed for sixty minutes, and of reagent and plasma for thirty minutes, while in specimens 76 to 100, coupling of the plasma and reagent was allowed for sixty minutes and of the serum and the reagent for thirty minutes. In neither of these groups could we detect any differences in readings not

⁵ Quoted from Hawk and Bergeim. *Practical Physiological Chemistry*, ed 9, Philadelphia, P. Blakiston's Son & Company, 1926, footnote, p. 396.

found in the group with coupling of equal duration. In fact, the largest difference in readings observed in the entire series, 0.8 unit, occurred in the group with equitemporal coupling (specimen 20).

An analysis of our figures (table 3) shows exact agreement in 70 per cent of our specimens. In the 30 per cent in which the readings did not agree, an approximately equal number of specimens showed

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4	0.1	0.4	54	3.1	3.2
5	0.5	0.4	55	0.2	0.2
6	No reaction	No reaction	56	1.1	1.0
7	6.2	6.2	57	0.3	0.3
8	4.9	5.0	58	0.2	0.2
9	1.3	1.2	59	1.8	2.0
10	1.0	1.1	60	0.5	0.5
11	1.0	1.0	61	1.5	1.5
12	0.3	0.3	62	0.1	0.2
13	0.4	0.3	63	0.2	0.2
14	5.5	5.6	64	0.2	0.2
15	7.5	7.5	65	0.1	0.1
16	8.3	8.2	66	0.1	0.1
17	10.0	10.4	67	5.3	5.2
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19	0.6	0.6	69	0.5	0.5
20	16.0	16.8	70	0.2	0.2
21	7.0	6.8	71	2.0	2.1
22	0.3	0.3	72	0.2	0.2
23	0.3	0.2	73	0.6	0.6
24	0.3	0.2	74	0.8	0.8
25	0.2	0.2	75	0.9	0.8
26	0.5	0.5	76	2.8	2.9
27	No reaction	No reaction	77	0.3	0.3
28	No reaction	No reaction	78	1.4	1.3
29	0.6	0.6	79	0.2	0.2
30	0.4	0.5	80	0.1	0.1
31	0.2	0.2	81	0.3	0.3
32	0.1	0.1	82	0.4	0.3
33	0.2	0.2	83	0.3	0.3
34	1.1	1.1	84	0.5	0.5
35	No reaction	No reaction	85	0.4	0.4
36	1.4	1.5	86	0.2	0.2
37	6.2	6.2	87	0.6	0.6
38	No reaction	No reaction	88	6.2	6.2
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41	1.0	1.0	91	0.3	0.4
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43	No reaction	No reaction	93	0.5	0.5
44	2.5	2.4	94	0.3	0.3
45	0.2	0.3	95	4.1	4.1
46	0.2	0.2	96	9.5	9.5
47	0.1	0.1	97	16.0	16.0
48	0.8	1.0	98	0.3	0.3
49	0.4	0.4	99	6.2	6.2
50	0.5	0.5	100	0.1	0.1

higher readings for the serum (in 16 per cent) and higher readings for the plasma (in 14 per cent), a division further borne out when the readings were grouped according to their magnitude. Thus in the group of readings between 0.6 and 1 unit, 66 per cent agreed exactly (eight of twelve readings), of the remaining 33 per cent (four of twelve), the reading for the serum was greater than that for the plasma

in two instances, and in two others the reading for the plasma exceeded that of the serum. In the group of from 5.1 to 10 units, the exact agreement was 55 per cent (seven of thirteen), equal numbers of those not agreeing were found to show greater readings for the serum than for the plasma and vice versa (three in each instance). In the other two groups, of from 1.1 to 5 and over 10 units, exact agreement

TABLE 3—*Agreement and Disagreement of the Readings for the Serum and the Plasma, One Hundred Cases*

Magnitude of Reading	All Readings	0.6 to 1 Units	1.1 to 5 Units	5.1 to 10 Units	Over 10 Units
Complete agreement (number)	70	8	5	7	1
Disagreement (number)	30	4	11	6	2
Serum readings greater (in units)	16	2	6	3	1
0.1	12	1	5	2	0
0.2	2	1	1	0	0
0.4	1	0	0	1	0
0.8	1	0	0	0	1
Average differences	0.175				
Plasma readings greater (in units)	14	2	5	3	1
0.1	11	2	4	2	1
0.2	3	0	1	1	0
Average differences	0.121				

TABLE 4—*Simultaneous Determinations of the Bilirubin in Quadruplicate, Five Cases*

Specimen Number	Plasma Reading, Units	Serum Reading, Units	Difference
37	6.4	6.3	0.1
	6.4	6.2	0.1
	6.2	6.2	0.0
	6.3	6.2	0.1
8	4.9	4.7	0.2
	4.7	4.4	0.3
	4.8	5.1	0.3
	4.6	4.8	0.2
78	1.4	1.6	0.2
	1.6	1.6	0.0
	1.5	1.6	0.1
	1.7	1.8	0.1
71	2.1	2.2	0.1
	2.0	2.3	0.3
	2.4	2.1	0.3
48	2.4	2.4	0.0
	0.8	0.6	0.2
	0.9	0.9	0.0
	1.1	0.8	0.3
	1.0	1.0	0.0
Average differences			0.141

occurred in but 31 and 33 per cent, respectively, the total numbers of specimens are, however, too small to draw any definite conclusions from these numbers. In each of these groups, further, a similar number showed a greater reading for the serum and a greater reading for the plasma (five and one, respectively). It is especially significant to us that, with but one exception (specimen 20), all readings differed by

no more than 0.4 unit. The largest number of differences occurred in the readings differing by 0.1 unit in each of the quantitatively separated subgroups.

To determine the probable error of our experiments, quadruplicate determinations were performed for five serums and plasmas taken at random from the specimens submitted (table 4). These determinations, when made with instruments (colorimeter, standards, chemicals and glassware), coupling conditions and conditions of lighting identical with those used in the entire series, and performed by one of us (R. K.), who performed the actual tests, showed differences ranging from 0 to 0.3 unit. In the entire series the differences were of the same order, from 0.1 to 0.4 unit, with but a single determination (specimen 20) showing a difference of 0.8 unit, a difference so much larger than the others observed as to warrant its omission from the series. Even with this large difference included, the average differences in the greater readings for the serum was 0.175 as compared with 0.121 in the greater readings for the plasma and 0.141 in the quadruplicate determinations. If this excessively large difference is omitted, these figures become 0.133, 0.121 and 0.141, respectively. The average differences between the greater readings for the serum and greater readings for the plasma then become of the order of magnitude as that in the groups for the quadruplicate determination, and the individual differences between the simultaneous readings for the bilirubin in the serum and in the plasma lose their apparent significance.

SUMMARY

- 1 The results of simultaneous quantitative determinations of bilirubin by the Thannhauser and Andersen modification of the van den Bergh technic in 100 consecutive and unselected cases are reported, and the results are analyzed as to the degree of agreement or disagreement.

- 2 The readings are shown to correspond in a very high degree, and they indicate that plasma instead of serum may be used with equal accuracy in determinations of bilirubin.

- 3 The results confirm the statements of McNee and Keefer. They are directly opposed to the figures reported by Shay and Schloss from eleven observations with wide discrepancies in the readings.

- 4 An increase in the length of time allowed for coupling up to one hour apparently plays no part in the slight quantitative differences noted.

THE FECES OF PATIENTS WITH CHRONIC ARTHRITIS ~

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AND

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That the gastro-intestinal tract of patients with chronic arthritis is abnormal in some way has long been assumed. Dietary regimens of all sorts have been proposed to correct faulty nutrition. Recent work of a clinical and experimental nature by A. A. Fletcher in Canada, R. McCarrison in England and R. Pemberton in the United States shows rather definitely that these people do best when their intake of vitamins is increased and their intake of carbohydrate reduced. Frequently the colon has been accused of acting as a focus of infection, to eradicate which it has been cleansed by vigorous catharsis or irrigation or by changing its bacterial flora, or it has been removed surgically.

If the intestinal tract is pathologic in any important degree, functionally or anatomically, it would seem that the feces, which are the result of the processes of digestion, absorption and motility, should contain some evidence of that fact. Strangely enough, no such data have been presented in the literature that we have examined. Acid stools are mentioned by some writers as being present in arthritis. Abnormal intestinal rates and "foul, evil-smelling feces" are also mentioned by others,¹ but no statistics of routine examinations on a series of patients are given. Therefore, the present study was undertaken to determine whether ordinary clinical laboratory tests reveal any abnormality in the stools of arthritic patients, and, if so, whether the abnormality be of one or of various types.

Our series consisted of forty patients at the Peter Bent Brigham Hospital, three of whom were seen in the medical wards and the rest in the arthritic clinic in the outdoor department, between October, 1929, and June, 1930. In each case the diagnosis was established by history and physical examination, routine analysis of the blood and urine and roentgenograms of the joints involved. Fifteen cases were considered to represent the so-called atrophic type of chronic arthritis, seventeen, the hypertrophic, and eight, a mixture of the two. Treatment was car-

² Submitted for publication, Sept. 26, 1930.

³ From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

¹ Pemberton, R. Arthritis and Rheumatoid Conditions, Philadelphia, Lea & Febiger, 1930.

ried out under the direction of one of us (F C H) It is beyond the scope of this paper to give the details of it, but the diet that was advised was always one rich in vitamins and rather low in available carbohydrates, totalling approximately 2,500 calories daily

At each visit each patient was asked to bring in a glass jar the last stool specimen passed, and the tests were all done by one man (R T M) Some patients were more faithful than others in complying with this request, and some were seen oftener than others, so that the number of stools from each person varied considerably Twelve patients had only 1 stool examined, but 142 specimens were analyzed in all The intervals between collection also varied considerably, depending on the need for seeing the individual patient Some cases were followed for only a short time, and others throughout the entire period of nine months Therefore, since much time is required in the treatment of this disease, no definite conclusions could be arrived at as to the effect of therapy on the character of the feces

The results are best presented according to the steps in a routine analysis of the stool—consistency, color, reaction, tests for blood and microscopic examination for parasites, starch, muscle fibers and fat

RESULTS OF EXAMINATION OF STOOLS

Consistency—The majority of the stools (86 of 142) were mushy and formless A few (5) were liquid, and the rest (51) were normally soft formed, fourteen of the latter, however, showed mushy areas Cathartics were a factor in only a few, since their use was denied in all but one case None was of the type seen in constipation

Color—The color was not unusual, except that the mushy stools tended to be rather lighter than the rest Diet and medication (spinach, carrots, iron) had a great influence on the stools in certain cases

Reaction—The reaction was tested by taking up a portion of the specimen on a throat stick and laying on it pieces of fresh red and blue litmus paper which had been moistened in tap water No attempt was made to determine the hydrogen ion concentration, as it appeared to offer no advantage over this simple and clinically sufficient method The normal stool so tested is usually neutral or alkaline In thirty-five (87.5 per cent) of these arthritic cases, there were one or more acid stools Of the total number of examinations, 91 (64 per cent) were acid, 35 (25 per cent) were neutral and 16 (11 per cent) were alkaline

Gas—In eighteen patients, all of whom had acid stools, the formation of gas could be observed grossly Bubbles were visible on the sides of the glass container, and when the mass was stirred with a throat stick, a crackling noise was made Generation was so active in several

instances as to blow off the cover when the catch was released. Nine of these patients complained of rumbling and gurgling noises in the abdomen or of an excess of flatus.

Miscellaneous—Benzidine and gum guaiac tests of occult blood were negative in all except one case, that of a woman in whom the duodenal ulcer had bled recently. Mucus was found in only a few specimens, and small in amount and apparently fresh. No parasites were discovered. Muscle fibers were well digested (rounded ends, absent striations) in all except two stools, which were liquid, probably the result of catharsis. No stool showed an excess of fat macroscopically or microscopically when stained with sudan III.

TABLE 1—*The Amount of Starch in the Stools of One Hundred and Forty-Two Specimens from Forty Patients with Chronic Arthritis as Compared with Ninety-Seven Specimens from Seventy-One Patients with Other Diseases*

Amount of Starch	Arthritic Group	Miscellaneous Group
None	0	22
Trace	5	31
+	25	18
++	39	19
+++	46	5
++++	27	2
Totals	142	97

Starch—The presence of an excess of starch was the most outstanding observation in these stools and deserves detailed comment. The method of examining the feces microscopically was as follows: a representative bit was rubbed up in a mortar with tap water to form a rather thin paste. The amount of water used varied, of course, with the consistency of the specimen. One drop of this paste was then placed on each of three glass slides, one was left unstained for a study of muscle fibers, parasites and soaps, sudan III was added to the second and a drop of compound tincture of iodine solution to the third. Cover slips were then applied to secure a thin film and allow the higher powers of the microscope to be used. Starch appears deep blue or black after the addition of iodine, erythrodextrin is red, and cellulose remains gray or black. Most of the starch in these cases was enclosed in vegetable cells, which have easily recognized contours, as shown in many works on clinical pathology. The rest of the starch was seen in the form of small, irregularly shaped masses, sometimes outlined by a trace of cellulose or else apparently free in the suspension. The liberation of this starch may have been due to breakage in the mortar.

It was found to be difficult to estimate the amount of starch with any degree of accuracy. Freshly passed stools from normal persons

on an unsalted diet usually show no iodine-staining lumps or only a few in the whole cover slip area when a fecal suspension of uniform density is made, as previously described. The latter was said to represent a trace. A larger amount (+) was roughly held to be 1 particle to every 5 or 6 high power fields, ++ was taken to be 1 in every high power field, +++, 2 to 5 in each field, and +++++, many lumps. On such a quantitative scale, none of the 142 stools from these 40 patients with chronic arthritis showed starch, 5 showed a trace, 25, +, 39, ++, 46, +++, and 27, +++++. If any amount under ++ is said to be not abnormal, 112 stools (79 per cent) still showed an excess of starch, which tended definitely to decrease in all cases in which there was improvement under treatment.

Iodine-Staining Organisms—These organisms appear as large cocci, round or oval, often in chains of four or six, and stain a deep blue or

TABLE 2—*The Relative Occurrence of Iodine-Staining Organisms and Positive Fermentation Tests in the Stools of Forty Patients with Arthritis and Sixty-One with Miscellaneous Diseases*

	Arthritic Group				Miscellaneous Group			
	No. of Cases	Per Cent	Stools	Per Cent	No. of Cases	Per Cent	Stools	Per Cent
Iodine staining organisms	36	90	93	65	16	22	17	17.5
Fermentation test positive	33	82.5	87	60	17	24	19	20

black with iodine. Their nature has not yet been determined. Years ago Schmidt² called them *Clostridia*, but he did not identify them further. Kendall³ associated them with the gas bacillus. Little attention has been paid to them, yet they seem to be intimately concerned with the presence of starch and gas in the stools.

Iodine-staining organisms were seen in the stools of 90 per cent of the arthritic patients in this series, only one examination was made in two of the other four cases and only two examinations in the other two. Ninety-three (65 per cent) of the 142 stools gave positive reactions. The number of these organisms did not vary in proportion to the amount of starch present. Sometimes they were found in enormous numbers in specimens with only a trace or a one plus amount of starch, and once they were absent when the starch was rated as four plus. Their presence proved to be a more reliable indication of a fermenting condition than an excess of starch. No specimen which contained starch

² Schmidt, A., and Strasburger, J. *Die Faeces des Menschen*, Berlin, August Hirschwald, 1903.

³ Kendall, A. I. *Intestinal Intolerance for Carbohydrates*, J. A. M. A. 86: 737 (March 13) 1926.

but not *Clostridia* produced gas, on the other hand, the production of gas was often most active with a little starch and many *Clostridia*. Usually, they were not found after the fermentation test, even though starch remained, and the reaction was still acid. After treatment, they tended to disappear much more slowly than the excess of starch.

Fermentation—Various methods have been devised for measuring the carbohydrate content of the feces, of which the simplest clinical test is that of Schmidt,² who used it to advantage in the diagnosis of fermentative diarrhea. This test was used in our work with certain modifications. The patients were not placed on the Schmidt test diet, instead, stools were accepted that were the result of an unselected diet, often rich in carbohydrates, or of a diet low in starch, after treatment was begun. The apparatus is similar to the Einhorn saccharometer, which is used for the detection of dextrose in the urine, except that it is larger and may be made of an ordinary glass jar and test tube connected by glass tubing. No attempt was made to measure the total amount of gas (carbon dioxide) found, if gas completely displaced the water in the collecting tube at the end of twenty-four hours' incubation and the reaction of the feces remained acid, the test was called positive. Therefore, while the following results may be considered as clinically informative, they cannot be judged according to Schmidt's rules. At first, all specimens were given this test. Later, as those which contained no starch or *Clostridia* were always found to be negative, they were not tested. Some specimens which gave neutral or even alkaline reactions, but which contained starch and *Clostridia*, gave positive reactions and became acid after incubation. One or more fermenting stools were found in thirty-three cases in this series (82.5 per cent). Since in the seven negative cases only ten stools were furnished, it was felt that a greater number of examinations might have increased this percentage. In all eighty-seven stools (60 per cent) gave positive reactions. The results did not correspond to those obtained for patients with any type of arthritis, the atrophic and hypertrophic forms being equally represented on both sides. There was a definite tendency for the test to become negative at a varying interval after treatment was begun. Even on direct questioning, few of the patients complained of symptoms suggesting a fermenting condition.

The question naturally arose whether the same disorder occurred with equal frequency among patients suffering from other chronic diseases. From his experience in the gastro-intestinal clinic in this hospital the impression obtained by one of us (R. T. M.) was that it was to be found only in patients with true fermentative diarrhea, in certain cases of migraine and rarely in a normal subject who has taken a great excess of starch. To obtain a more definite answer to this

question, however, stools were collected from seventy-one patients in the medical wards, and examined as before. No selection of cases was made. Many types of disease were represented, 10 patients had some form of heart disease, 14, chronic nephritis, 11, peptic ulcer, 11, an acute infection (pneumonia, tonsilitis), 5, pulmonary tuberculosis, 4, cancer, 2, pernicious anemia, and 15, miscellaneous conditions (hyperthyroidism, myxedema, abscess of the lung, etc.). Diet was restricted in only a few cases. It was usually an ordinary "balanced" ration, often containing an increased amount of carbohydrates to force nourishment.

Of the ninety-seven stools examined, one-third were acid (35), one-third neutral (31) and one-third alkaline (31). Twenty-two showed no starch, 31, a trace, 18, +, 19, ++, 5, +++, and 2, ++++. Only 26.8 per cent showed a reaction of ++ or more, as compared to 79 per cent for the arthritic group. Iodine-staining organisms were found in 17 stools (17.5 per cent) in 16 cases (22.5 per cent), roughly one-fourth the frequency in the other group. Fermentation tests gave positive reactions in 19 stools (20 per cent) from 17 patients (24 per cent). This test became negative in all 6 cases in which more than a single stool was examined, and *Clostridia* also disappeared more quickly than from the stools in the first group.

Certain definite conclusions are suggested by these figures, even though the numbers of cases and examinations are small. If inability to utilize starch is shown by its appearance in the stool to excess, by the presence of *Clostridia* and by the formation of gas, then it is relatively uncommon among patients suffering from ordinary chronic or acute disease. It occurs frequently enough, however, to give rise to the speculation that it may occur rather easily from slight causes and may clear up readily when these causes are removed. However, inability to utilize starch is found in the great majority of patients with chronic arthritis, and responds sluggishly to treatment. It would seem to be a definite disorder in these patients, since it does not react quickly to the amount or type of carbohydrate in the diet.

The significance of this observation is not apparent. Much work remains to be done to verify and explain it. Possibly it may point to an abnormal condition of the intestinal mucosa comparable to that of other tissues in the body in arthritis. In animals McCarrison⁴ produced organic changes in the intestines and elsewhere by feeding diets deficient in vitamins and high in starch. By roentgen examination and barium enema Fletcher⁵ found a decrease in haustral markings, loss of tone and lengthening of the colon in his arthritic patients whose nutrition

⁴ McCarrison, R. Brit. M. J. 2 730, 1926.

⁵ Fletcher, A. A. and Graham, D. Am. J. M. Sc. 179 91, 1930.

had been faulty for a long time, and he felt that this was evidence that the experimental observations held true for man. Our results tend to support his views.

SUMMARY

1 One hundred and forty-two stools from forty patients with chronic arthritis were analyzed in a simple routine way, and the results were compared with those obtained on examination of ninety-seven stools from seventy-one patients suffering from various other diseases.

2 No definite pathologic condition was found, except for the presence of starch in the stools from the arthritic group of patients. (a) Seventy-nine per cent of the stools showed an excess of starch, as compared with 26.8 per cent for the control group. (b) Iodine-staining organisms were found in the stools of 90 per cent of the patients, as compared to 22 per cent for the controls. (c) The fermentation test was positive in 82.5 per cent of the cases, as compared to 24 per cent for the controls.

3 Difficulty in the utilization of starch, while occasionally found in a variety of conditions, is prone to occur in patients with chronic arthritis, and adds further evidence that diets low in starch are of use in this disease.

THE TREATMENT OF PERNICIOUS ANEMIA WITH DESICCATED HOG'S STOMACH¹

PROF I SNAPPER, M D

AND

J D G DE PREEZ, M D

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Since Cahn and von Mehnig in 1886, first drew attention to the absence of hydrochloric acid in a case of pernicious anemia it has gradually become recognized that this association is practically a *conditio sine qua non*

On the continent of Europe this subject has been investigated chiefly by Faber, Ewald, Zadek, Wernberg and others, Faber expressing as his opinion that achylia gastrica is generally preceded by a chronic gastritis. In England Hurst was the chief exponent, he also showed by means of the fractional test meal that the absence of free hydrochloric acid in pernicious anemia invariably persists throughout the whole period of digestion, whereas in other conditions such as cancer of the stomach, it is not uncommon to find a small quantity of free acid in one or more of the fractions

The significance of this achylia was pointed out by Castle¹ who in a series of experiments with normal gastric juice and beet muscle administered in different ways to patients with pernicious anemia, endeavored to establish an etiologic relationship between achylia gastrica and pernicious anemia. This constant achylia and the facts concerning the familial occurrence of pernicious anemia as well as the frequency of achylia among relatives of patients suffering from this disease, constituted the fundamental thoughts that gave him the impetus to these experiments

The work of Castle was the principal inducement to Sharp,² Sturgis and Isaacs,³ and Conner⁴ to treat patients for pernicious anemia by feeding them raw and desiccated hog's stomach. These workers came to the conclusion that stomach tissue per gram of fresh material is even

¹ Submitted for publication, Aug 21, 1930

¹ Castle Brit M J **1** 1120, 1929, Am I M Sc **178** 748, 1929 Castle and Townsend Ibid **178** 764, 1929

² Sharp, E H Antianemic Factor in Desiccated Stomach, J A M A **93** 749 (Sept 7) 1929

³ Sturgis, C S, and Isaacs, R Desiccated Stomach in the Treatment of Pernicious Anemia, J A M A **93** 747 (Sept 7) 1929

⁴ Conner, H M Treatment of Pernicious Anemia with Swine Stomach, J A M A **94** 388 (Feb 8) 1930

more active than liver, as a smaller amount of the former is required to induce a remission in the patient with pernicious anemia.

It was therefore considered necessary to carry out a series of experiments to verify this new treatment for pernicious anemia. If corroborated, this new method of treatment not only would be a medical discovery of great importance but would replace the more expensive liver therapy.

We have thus far observed thirty patients treated with desiccated hog's stomach. For this purpose a Dutch pharmaceutical company placed their experimental supplies of desiccated hog's stomach at our disposal. The mode of preparation is as follows. The organs of

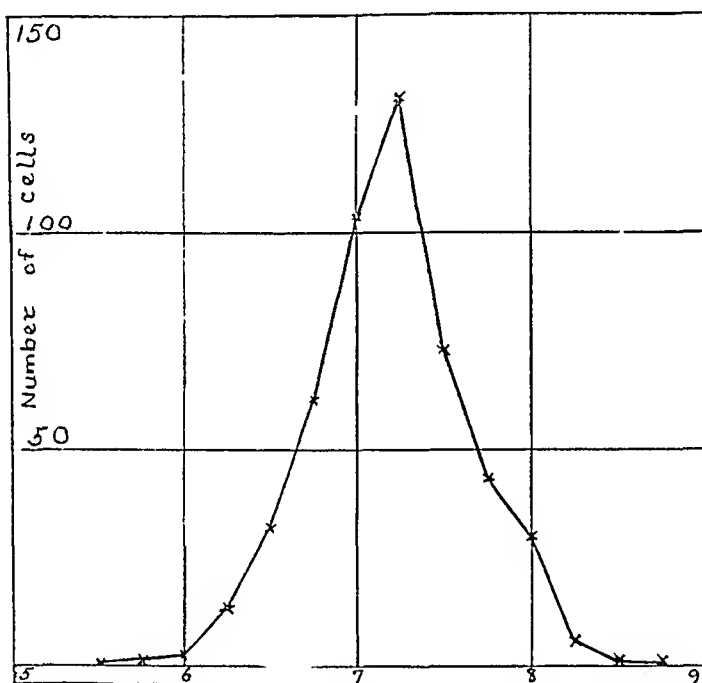


Chart 1—Average Price-Jones curve of two normal persons, 500 cells in each instance

healthy animals are taken from the body immediately after the slaughter and thoroughly and repeatedly washed in running water. The inside surfaces are then mechanically cleaned by means of a hard brush and the whole stomachs subsequently ground in a meat chopper to a fine pulp. The pulp is spread in thin layers on aluminum plates and placed in a special vacuum desiccator at temperatures ranging from 35 to 45 C. The organs dried by this method are then subjected to a process for the extraction of fat and finally pulverized.

The daily dosage varied from 3 to 6 spoonfuls (5 Gm.), it was usually administered before meals in lemonade or soup or mixed with porridge or other food.

Pence-Jones' method of measuring the diameters of the red blood cells was employed in order to control the results of the treatment, as embodied in the appended charts, the megalocytosis and anisocytosis, as well as the improvement in the course of the treatment, are shown.

The influence of the administration of the stomach extract was controlled by reticulocyte counts, the reticulocytosis usually appeared about the fifth day after the treatment was started, and reached its maximum at about from the tenth to the twelfth day. The accompanying curves represent the number of reticulocytes per thousand erythrocytes, the number of red blood cells and the percentage of hemoglobin.

REPORT OF CASES

CASE 1—J. H., a trader, aged 44, complained of lassitude and loss of energy for a year, so that he was unable to carry on his work. He had become pro-

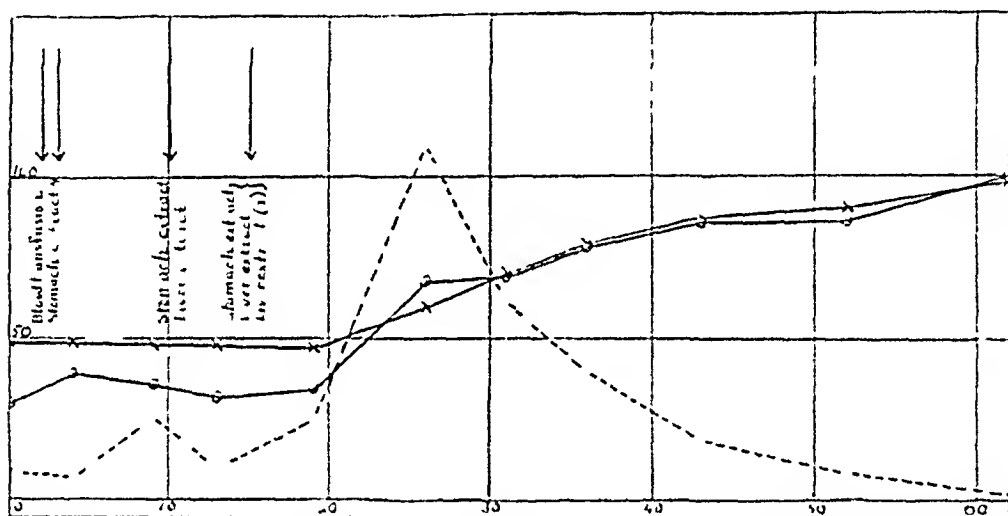


Chart 2 (case 1) —Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line). Liver extract (1) was given according to the method of Castle and Bowie.

gressively worse and had noticed that he was becoming paler and anemic. There were dyspnea on slight exertion and a history of much indigestion, however, there was no diarrhea. He also complained of soreness of the tongue. There was no tingling and numbness in the hands and feet. During the last month he had been treated with liver, with negative results.

Examination revealed pale yellow sclerae and a pale yellow skin, the teeth were carious, the tongue was smooth and atrophic. At the apex of the heart a slight systolic murmur was heard. The liver was not enlarged, and the spleen was just palpable. No other abnormalities were found.

Examination of the urine revealed no albumin or bilirubin, the test for urobilin was strongly positive. A blood count showed hemoglobin, 48 per cent erythrocytes, 2,010,000, color index, 12, white blood cells, 4,900, reticulocytes, 14 per thousand erythrocytes, platelets scanty, anisocytosis, poikilocytosis, polychromatophils and punctate basophilia, normoblasts and megaloblasts. The indirect van den Bergh test showed 20 mg of bilirubin per liter of serum, the Was-

sermann test of the blood was negative. Fractional gastric analysis showed achylia. In the feces spectroscopic examination revealed no blood.

A tablespoonful of stomach extract was given four times a day. After a fortnight there was no improvement, and a transfusion of 500 cc of blood was given. A week later, a liver extract was given four times a day in addition to the stomach extract. The patient did not react satisfactorily until he was also given liver extract according to the method of Castle and Bowie. Eleven days later, examination showed hemoglobin, 60 per cent, erythrocytes, 3,400,000, and reticulocytes, 110 per thousand. Improvement was progressive, so that one month later the hemoglobin was 98 per cent and the erythrocytes numbered 5,000,000.

In this case it is difficult to state definitely what the essential part of the treatment was, it may have been the blood transfusion. We think that

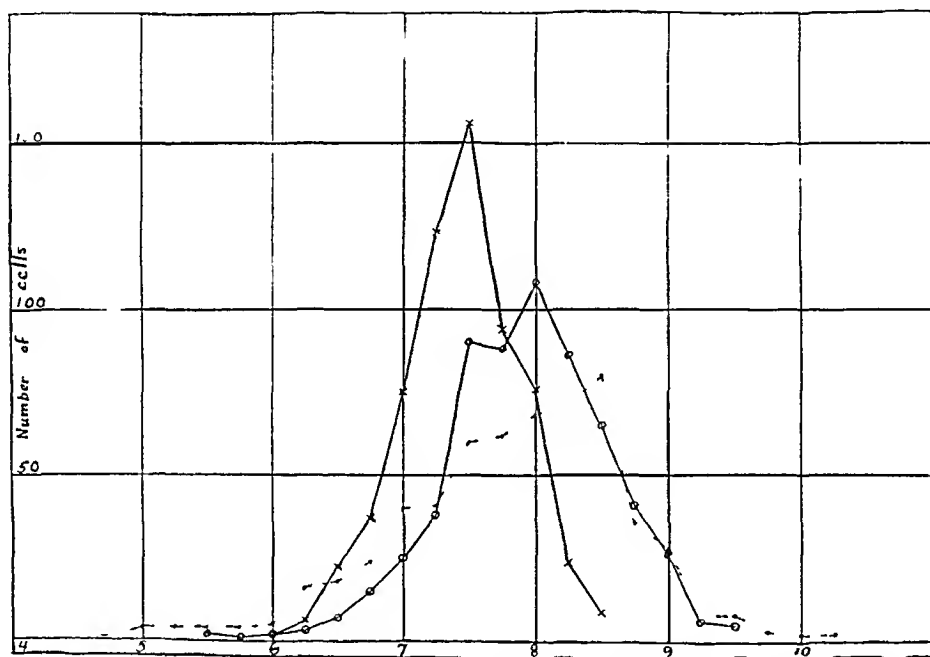


Chart 3 (case 1) —Price-Jones curves, each of 600 cells. On December 13 (dotted line) hemoglobin was 49 per cent and erythrocytes 1,510,000, on January 23 (circles), hemoglobin 87 per cent and erythrocytes 4,290,000, on February 18 (crosses), hemoglobin 98 per cent and erythrocytes 5,000,000.

the initial dosage of stomach extract was far too small for a severe case. The three Price-Jones curves (chart 3) clearly show how the blood picture became almost normal morphologically.

CASE 2—H. E., a woman, aged 66, engaged in housework, had been healthy until a year before examination, when she began complaining of weakness, lack of energy, pallor and tingling and numbness in the toes, so that she was unable to do her daily work. She also complained of pain in the tongue and palpitation of the heart on exertion. She had no diarrhea, but gave a history of occasional indigestion and slight edema of the ankles.

Examination revealed anemic conjunctivae, the sclerae were not jaundiced, the tongue was reddish and smooth, and the teeth were poor. The skin had a pale

yellowish tinge. No other abnormality was found, except that the liver was just palpable.

The urine contained a trace of albumin but no bilirubin, the test for urobilin, however, gave strongly positive results. A cytologic examination showed hemoglobin, 50 per cent, red blood cells, 1,850,000, color index, 1.2, leukocytes, 4,100, reticulocytes, 2 per thousand, platelets, 60,000, poikilocytosis, anisocytosis and

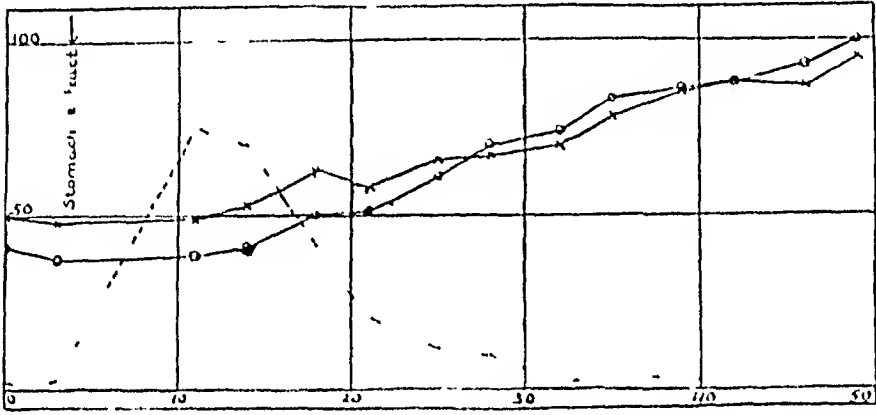


Chart 4 (case 2) —Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dotted line)

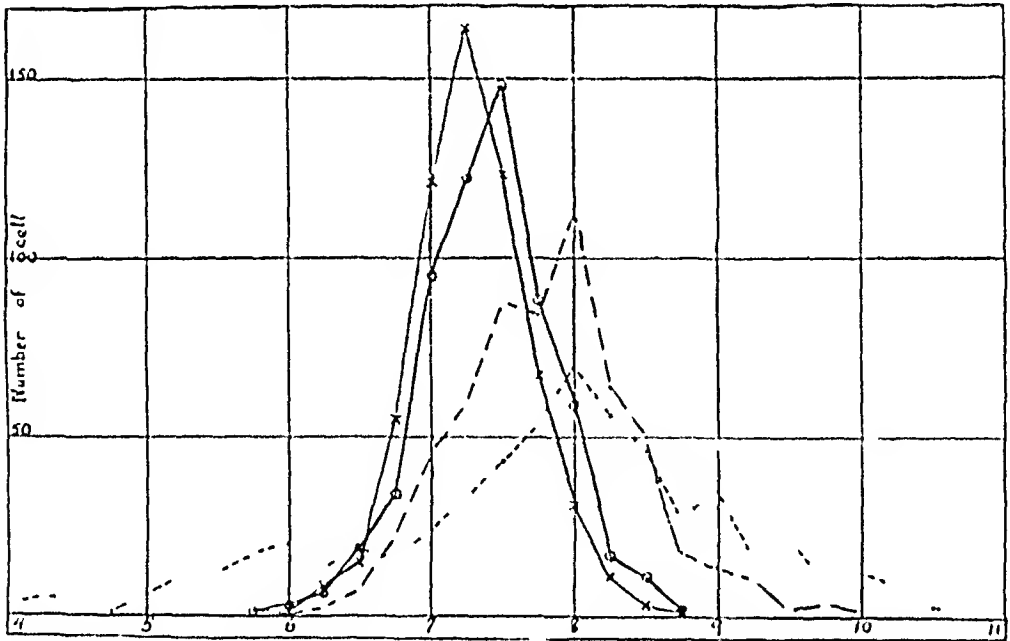


Chart 5 (case 2) —Price-Jones curves, each of 600 cells. On Nov. 14, 1929 (dotted line), erythrocytes were 1,850,000 and hemoglobin 50 per cent, on Jan. 3, 1930 (dot and dash), erythrocytes 4,500,000 and hemoglobin 95 per cent, circle line shows condition one month later, on June 26 (crosses), hemoglobin 100 per cent.

polychromatophilia, normoblasts but no megaloblasts. The direct van den Bergh test gave negative results, the indirect test showed 12 mg. of bilirubin per liter of serum. Fractional gastric analysis revealed no free hydrochloric acid, the

highest total acidity was 15. The blood pressure was 170 systolic and 75 diastolic, the Wassermann and Sachs-Georgi tests of the blood were negative. The feces contained no blood.

A tablespoonful of stomach extract was given three times a day. In about ten days the reticulocytes had increased to about 80 per thousand, at the same time

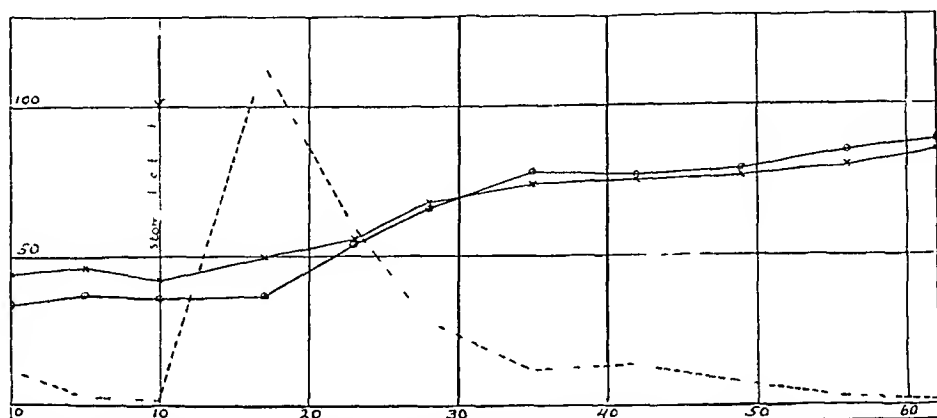


Chart 6 (case 3) —Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line)

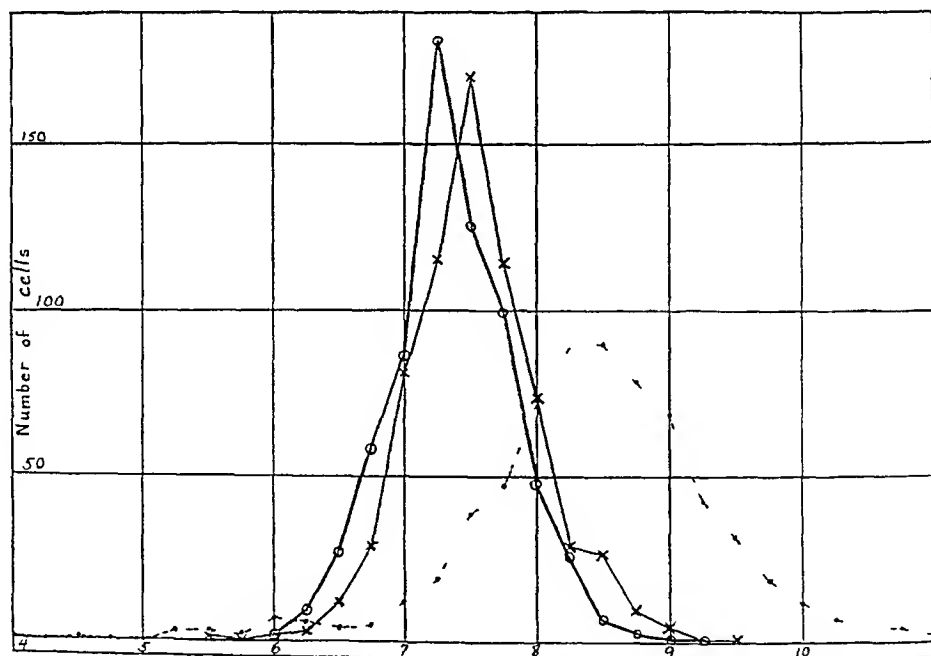


Chart 7 (case 3) —Price-Jones curves, each of 673 cells. On Dec 7, 1929 (dotted line), erythrocytes were 1,610,000 and hemoglobin 44 per cent, on Feb 5, 1930 (crosses), erythrocytes 4,400,000 and hemoglobin 85 per cent, four months later (circles), hemoglobin 102 per cent

the hemoglobin and the number of red blood cells showed similar improvement, so that after treatment for forty-five days the blood picture showed hemoglobin, 95 per cent, erythrocytes, 4,510,000, and the color index, 0.95.

In this case the use of stomach extract was a complete success, as is evidenced by the four Price-Jones curves (chart 5)

CASE 3—J. T., a farmer, aged 64, complained of progressive loss of energy, dyspnea on exertion and general weakness. The skin had gradually become pale and yellowish. During the last few months preceding examination his legs had become stiff and walking difficult. He had no pain in the tongue, but often had a burning sensation in the mouth. The appetite was good, there was, however, a history of flatulence and indigestion, but no diarrhea.

On examination, the skin was a pale yellow, no cyanosis or dyspnea was present. The conjunctivae were anemic and the sclerae slightly jaundiced. The teeth were in a poor condition. Examination of the chest and abdomen revealed nothing abnormal. Definite medullary symptoms were present.

A test of the urine for urobilin gave strongly positive results. The blood count showed hemoglobin, 44 per cent, erythrocytes, 1,610,000, color index, 1.3, leukocytes, 5,800, reticulocytes, 7 per thousand, anisocytosis, poikilocytosis, polychromatophilia and punctate basophilia, normoblasts and a few megaloblasts. The Wassermann and Sachs-Georgi tests of the blood were negative. The indirect van den Bergh test showed 186 mg. of bilirubin per liter of serum.

A tablespoonful of stomach extract was given five times a day. After about seven days a strong reticulocytosis (114 per thousand) was observed. The improvement thereafter was progressive, the urobilin gradually disappearing from the urine. At the end of about fifty days the blood picture showed hemoglobin 85 per cent, and erythrocytes, 4,400,000.

In this case also the new treatment was successful. The Price-Jones curves (chart 7), made at the beginning and at the end of the treatment in the hospital and five months later, are among the best in this series. The symptoms in the spinal cord showed little or no improvement.

CASE 4—J. R., a woman, aged 31, engaged in housework, enjoyed good health until about eight years before examination, when after the birth of a child she began complaining of general weakness and loss of energy. During the past year these complaints had become progressively worse, so that she was finally unable to do her housework. There was also soreness of the tongue, especially when she ate sour things.

Examination revealed carious teeth, the tongue was smooth and atrophic. The conjunctivae were anemic, while the sclerae had a touch of jaundice. Examination of the chest and abdomen revealed nothing abnormal, except that the liver was just palpable.

A test of the urine for urobilin was strongly positive. Examination of the blood showed hemoglobin, 52 per cent, erythrocytes, 1,900,000, color index, 1.2, white blood cells, 4,100, reticulocytes, 6 per thousand, blood platelets scanty (82,000), anisocytosis, poikilocytosis and marked punctate basophilia, normoblasts and 2 megaloblasts. The indirect van den Bergh test showed 222 mg. of bilirubin per liter of serum. Fractional gastric analysis gave no free hydrochloric acid, the highest total acidity was 12. No blood was demonstrable in the feces spectroscopically or otherwise. The fundus was normal in both eyes. The Wassermann and Sachs-Georgi reactions were negative.

Treatment consisted of a tablespoonful of stomach extract three times a day, and dilute hydrochloric acid and pepsin. Within ten days the reticulocytosis

reached its maximum (140 per thousand) At the same time the hemoglobin and the red blood cell count began to improve, so that at the end of forty days the blood count showed hemoglobin, 90 per cent, erythrocytes, 4,240,000, and color index, 0.95 The urine contained no urobilin Fractional gastric analysis showed no free hydrochloric acid

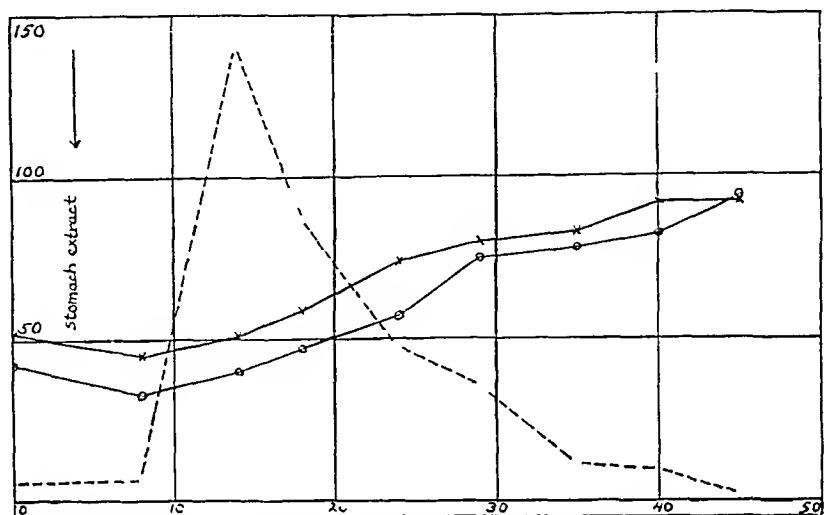


Chart 8 (case 4) —Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line)

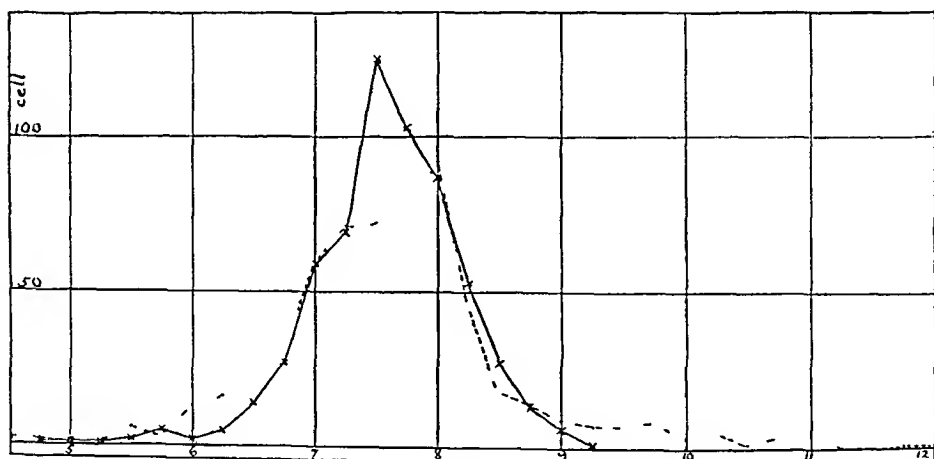


Chart 9 (case 4) —Price-Jones curves, each of 500 cells On Dec 4, 1929 (dotted line), erythrocytes were 1,900,000 and hemoglobin 52 per cent, on Jan 18, 1930 (crosses), erythrocytes 4,240,000 and hemoglobin 90 per cent

CASE 5—F v d S, a woman, aged 56, engaged in housework, had been well until three years before examination, when she began to complain of general lassitude, loss of energy, vomiting and other symptoms of indigestion She had pain in the tongue and ate poorly She had become progressively paler and suffered from palpitation of the heart on the least exertion

On examination the conjunctivae appeared to be anemic, the sclerae had a yellowish tinge There was no dyspnea or cyanosis The teeth were artificial

The tongue contained grooves in the middle and was smooth along the sides. The heart was enlarged two fingerbreadths to the left, systolic murmurs were heard at all ostia. The liver was palpable about three fingerbreadths from the costal margin, the spleen was just palpable.

The urine contained a trace of albumin, the test for bilirubin was negative and that for urobilin, strongly positive. Examination of the blood showed hemo-

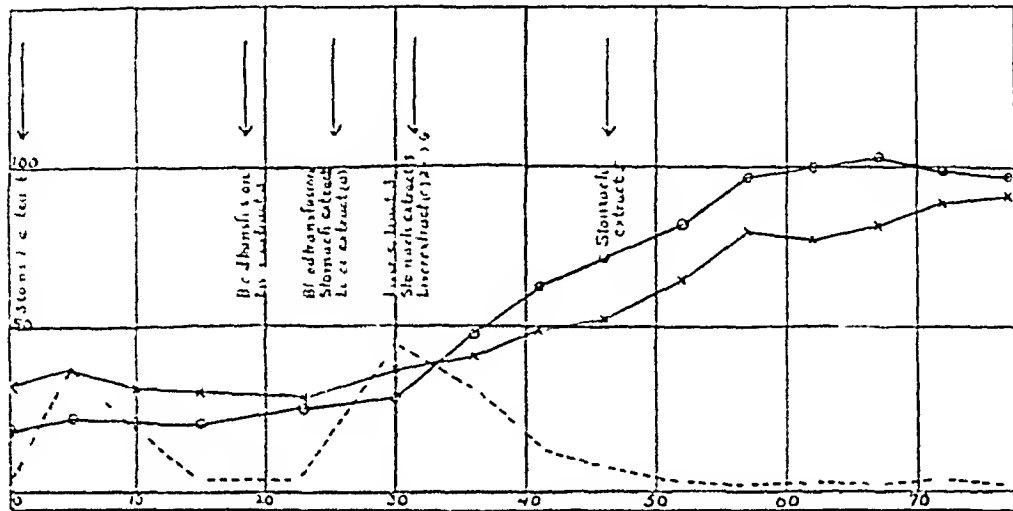


Chart 10 (case 5) —Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line). Liver extract (1) was made from 250 Gm. of fresh liver.

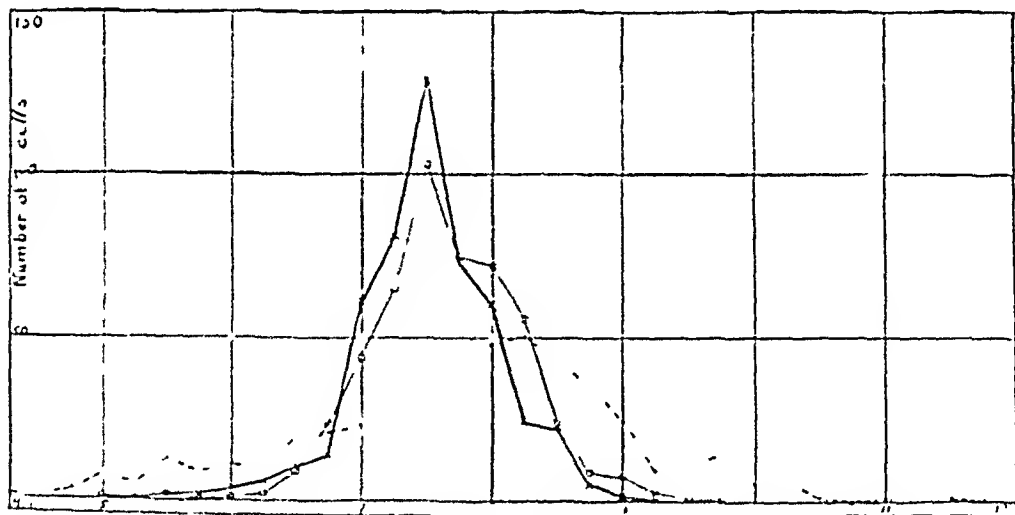


Chart 11 (case 5) —Price-Jones curves, each of 500 cells. On Dec 22, 1929 (dash line), erythrocytes were 850,000 and hemoglobin 33 per cent, on Feb 2, 1930 (circles), erythrocytes 4,390,000 and hemoglobin 90 per cent, on March 12 (crosses), erythrocytes 4,360,000 and hemoglobin 91 per cent.

globin, 33 per cent, erythrocytes, 850,000, color index, 1.6, leukocytes, 2,900, reticulocytes, 3 per thousand, blood platelets, 40,000, marked anisocytosis, poikilocytosis, polychromatophilia and punctate basophilia, several normoblasts and megaloblasts. The indirect van den Bergh test yielded 22 mg of bilirubin per

liter of serum. The Wassermann and Sachs-Georgi tests of the blood were negative. The feces contained no blood. Fractional gastric analysis revealed no free hydrochloric acid.

Treatment consisted of a tablespoonful of stomach extract three times a day and dilute hydrochloric acid and pepsin. In three weeks the general condition of the patient had become worse and it was therefore decided to give a blood transfusion of 500 cc. The administration of stomach extract was stopped and instead liver extract was given, five times a day. Six days later, another blood transfusion of 500 cc. was given. Stomach extract was given three times a day in addition to the liver extract. Five days later there was a slight reticulocytosis (45 per thousand). It was decided, however, to add another liver extract, made from 250 Gm. of fresh liver. From then on there was decided improvement, so that fourteen days later the blood count showed hemoglobin, 53 per cent, and erythrocytes, 3,280,000.

The liver extracts were removed from the treatment, the patient now being given only stomach extract, a spoonful five times a day. Improvement was continuous, a month later, the blood count was hemoglobin, 91 per cent, and erythrocytes, 4,360,000.

In this case there is no doubt that the initial dosage of stomach extract (a tablespoonful three times a day) was far too small. The three Price-Jones curves (chart 11) illustrate the morphologic improvement in the red blood cells.

CASE 6—A. B., a housewife, aged 34, complained of weakness, lack of energy and pallor for two years. The onset of symptoms had been insidious, but they had become most pronounced eighteen months before examination, when the hemoglobin was only 15 per cent. She had pain in the tongue, but never suffered from diarrhea or from tingling and numbness in the fingers and toes. She was then residing in Germany and was treated with a liver preparation given for pernicious anemia. The hemoglobin content returned to 63 per cent. She continued to use the liver preparation, but after a few months her condition again became worse. A German preparation of desiccated hog's stomach caused some improvement but later the condition became progressively worse.

On examination the skin was a lemon yellow, the sclerae were slightly jaundiced, the conjunctivae showed extreme anemia. The teeth were carious. The tongue was smooth and atrophic. Examination of the chest revealed anemic murmurs at all ostia; otherwise observations were normal. The liver and spleen were both just palpable.

A test of the urine for urobilin gave strongly positive results. Examination of the blood showed hemoglobin, 38 per cent, erythrocytes, 1,900,000, color index, 0.9, leukocytes, 2,600, reticulocytes, 6 per thousand, marked anisocytosis, poikilocytosis, punctate basophilia and polychromatophilia, many normoblasts and a few megaloblasts, platelets scanty. The direct van den Bergh test gave negative results, the indirect test showed 9 mg. of bilirubin per liter of serum. The Wassermann reaction of the blood was negative. No blood was demonstrable in the feces spectroscopically or otherwise.

Treatment consisted of a tablespoonful of stomach extract given six times a day and dilute hydrochloric acid and pepsin. Twelve days later there was a strong reticulocytosis (204 per thousand). The improvement was progressive, so that after about fifty-three days the hemoglobin was 90 per cent and the erythrocytes numbered 4,750,000.

The color index was never greater than 1, nor was the Price-Jones curve (chart 13) typical at the beginning. Improvement under the administration of hog's stomach was no less striking, however, than in the other cases.

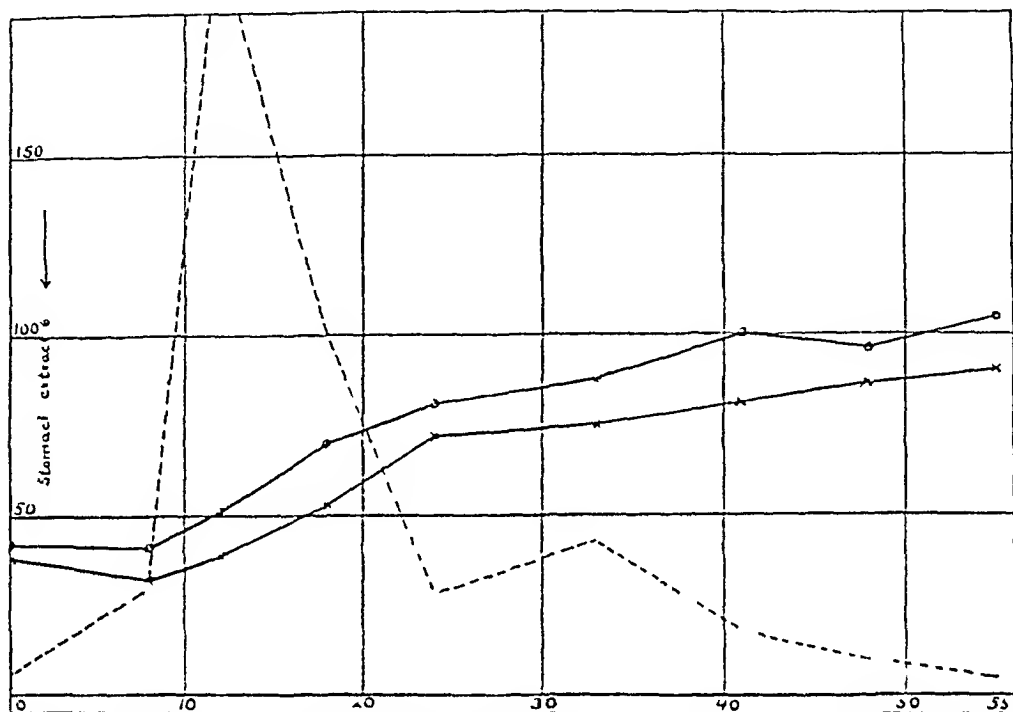


Chart 12 (case 6) —Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line)

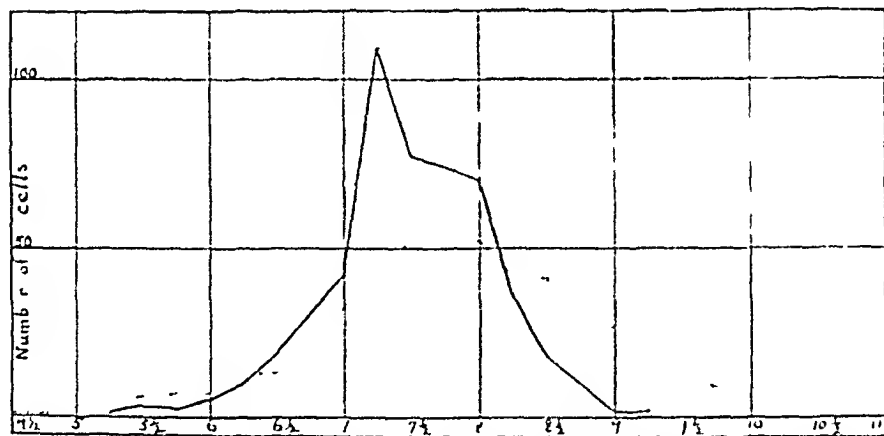


Chart 13 (case 6) —Price-Jones curves, each of 500 cells. On March 8, 1930 (solid line), erythrocytes were 1,900,000 and hemoglobin 38 per cent, on May 2 (dotted line), erythrocytes 4,570,000 and hemoglobin 90 per cent.

CASE 7—J. P., a printer, aged 62, was healthy until two years before examination, when he started to complain of grooves in the tongue which caused him much pain. Thereafter he began to complain of weakness. He got up tired and went to bed tired, so that at last he was unable to remain at his work. A year

before, he underwent treatment with liver, and the hemoglobin percentage rose from 30 to 80. Liver therapy was then discontinued, and twelve weeks later his condition was as poor as before.

On examination, the skin was of a lemon-yellow color, the conjunctivae were anemic. The tongue showed deep grooves in the middle, and was smooth along the sides. The teeth were poor. Examination of the chest and abdomen revealed nothing abnormal, except that both the liver and the spleen were just palpable.

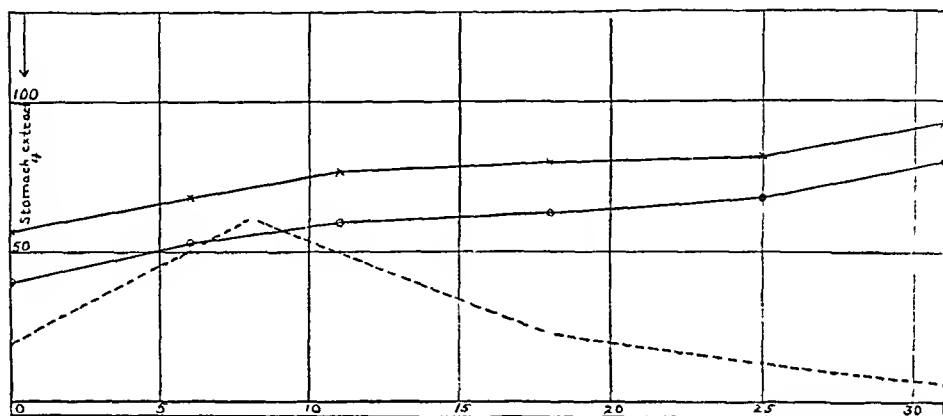


Chart 14 (case 7) —Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line)

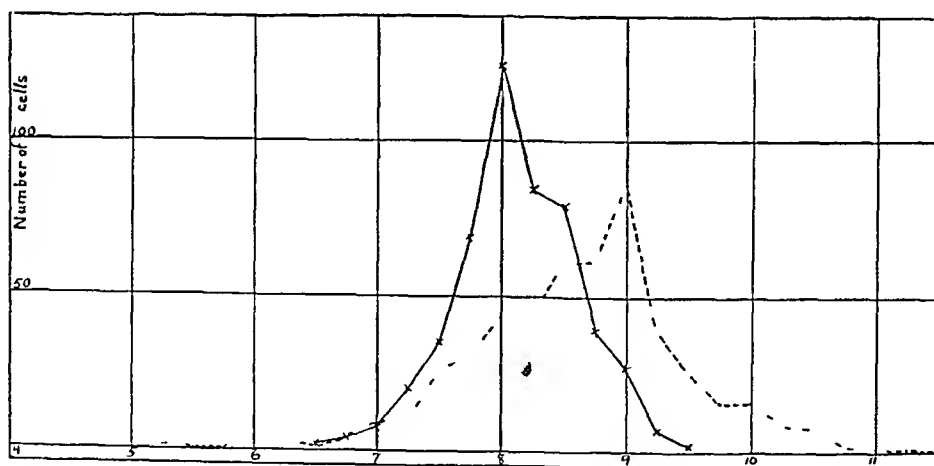


Chart 15 (case 7) —Price-Jones curves, each of 500 cells. On April 6, 1930 (dotted line), erythrocytes were 2,000,000 and hemoglobin 57 per cent, on May 7 (crosses), erythrocytes 4,020,000 and hemoglobin 93 per cent.

A test of the urine for urobilin gave strongly positive results. The blood picture showed hemoglobin, 57 per cent, erythrocytes, 2,000,000, color index, 14, leukocytes, 4,900, reticulocytes, 19 per thousand, anisocytosis, poikilocytosis and polychromatophilia, 1 megaloblast and several normoblasts, blood platelets clearly diminished.

A tablespoonful of stomach extract was given four times a day. Between the sixth and eleventh days a reticulocytosis of about 60 per thousand was found,

the general condition improved so that, after a month's treatment, the hemoglobin was 93 per cent and the red blood count, 4,020,000

CASE 8—T V, a man, aged 56, had complained of weakness, loss of energy and palpitation of the heart for three and a half years. At the onset of the condition he began to look pale and lost considerable weight. He was sent to the south of France, and while there was treated with liver. Thereafter he was again able to do his work. Gradually, however, his condition became worse and

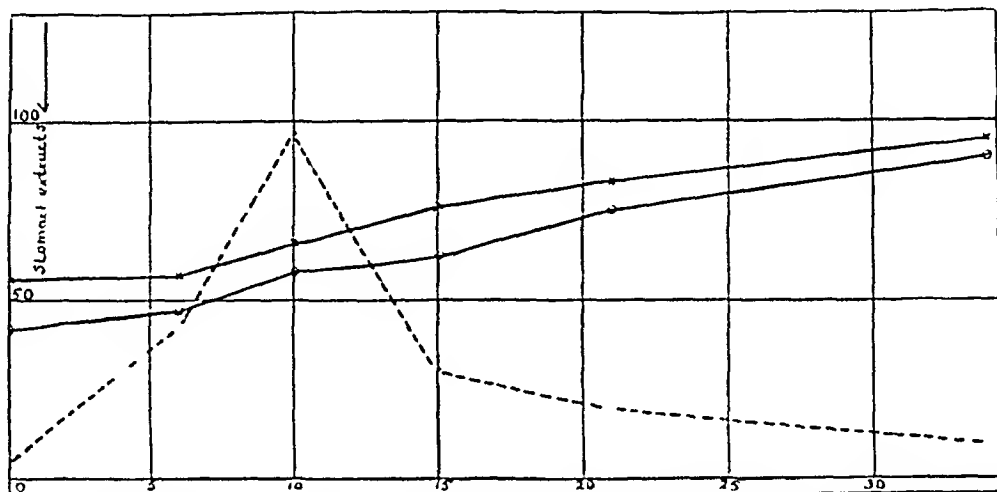


Chart 16 (case 8) —Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line)

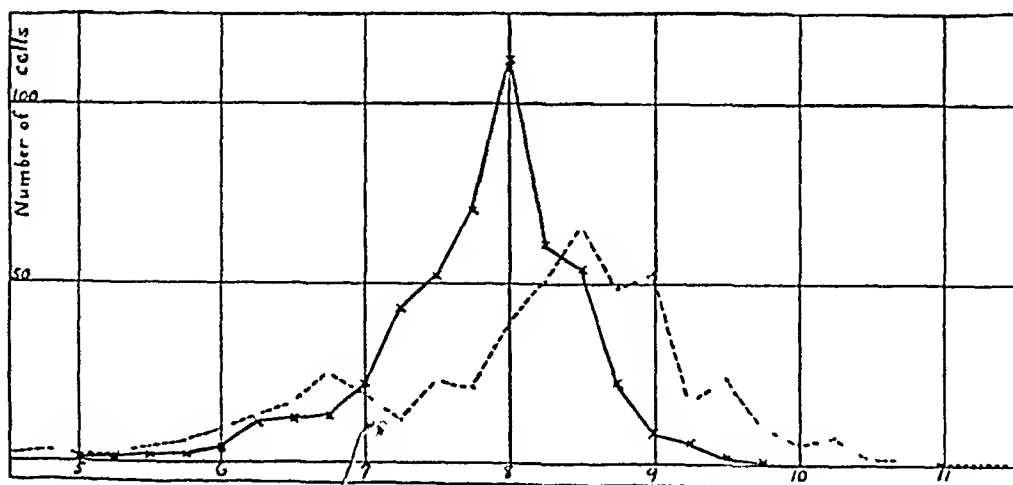


Chart 17 (case 8) —Price-Jones curves, each of 500 cells. On April 2, 1930 (dash line), erythrocytes were 2,000,000 and hemoglobin 56 per cent, on May 6 (crosses), erythrocytes 4,400,000 and hemoglobin 95 per cent

diarrhea developed. He was again treated with liver and for a year he was able to attend to his work. Thereafter liver therapy was ineffective. He became progressively worse, had pain in the tongue and complained of tingling and numbness in the fingers.

On examination, the skin was of a lemon-yellow color. The conjunctivae were anemic, the sclerae were not jaundiced. The teeth were poor, and the

tongue smooth and atrophic. Further examination of the chest and abdomen revealed a palpable liver and spleen.

The urine contained no bilirubin, the test for urobilin was strongly positive. Examination of the blood showed hemoglobin, 56 per cent, erythrocytes, 2,000,000, color index, 1.3, leukocytes, 4,700, reticulocytes, 4 per thousand, anisocytosis, poikilocytosis, polychromatophilia and punctate basophilia, several normoblasts. No blood was found in the feces.

A tablespoonful of stomach extract was given five times a day. Ten days after the treatment was begun, the reticulocytosis had reached its maximum (96 per thousand). The patient's condition continued to improve generally, so that after thirty-five days, examination of the blood revealed hemoglobin, 95 per cent, and erythrocytes, 4,400,000.

The morphologic improvement is evidenced by the Price-Jones curves at the beginning and at the end of the treatment (chart 17). It will be

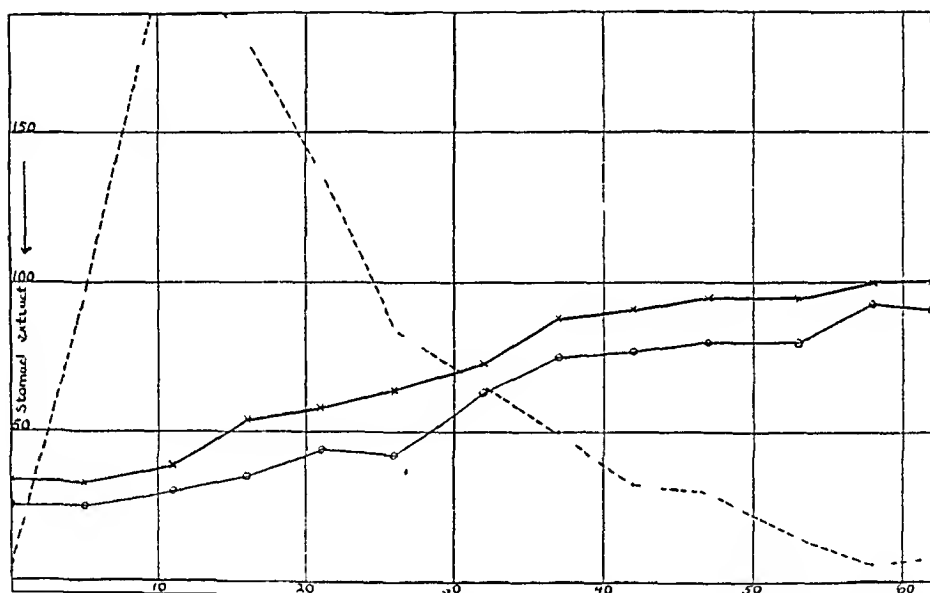


Chart 18 (case 9) —Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line)

noticed, however, that there still existed considerable megalocytosis, a condition that evidently does not run parallel with improvement in hemoglobin and red blood count.

CASE 9—G B a woman aged 59, engaged in housework, complained of weakness in the legs and general lassitude for eight months. The last few months before examination her condition became much worse and she began to look pale. There was a history of indigestion and occasional vomiting. There was no soreness of the tongue or any unusual feeling in the hands or feet.

On examination, the skin showed a lemon-yellow pallor. The conjunctivae were anemic and the sclerae slightly jaundiced. The tongue was not smooth, the teeth were in a poor condition. The area of cardiac dulness was somewhat enlarged in both directions, systolic murmurs were heard at all ostia. Further examination of the chest, abdomen and extremities showed nothing abnormal.

The urine contained a trace of albumin but no bilirubin, tests for urobilin gave strongly positive results. Examination of the blood showed hemoglobin, 34 per cent, erythrocytes, 1,160,000, color index, 1.3, white blood cells, 3,000, reticulocytes, 9 per thousand, platelets, 80,000, marked anisocytosis, poikilocytosis, polychromatophilia and punctate basophilia, several normoblasts and 3 megaloblasts in 100 white blood cells. The direct van den Bergh test gave negative results, the indirect test showed 11.2 mg of bilirubin per liter of serum. The blood pressure was 150 systolic and 60 diastolic. The Wassermann and Sachs-Georgi tests of the blood were negative. The feces contained no blood. Fractional gastric analysis revealed no free hydrochloric acid.

A tablespoonful of stomach extract was given six times a day. A marked reticulocytosis (215 per thousand) was noted about the eleventh day. From then on the hemoglobin percentage and red blood count gradually improved, so that, after treatment for two months, examination showed hemoglobin, 100 per cent, and erythrocytes, 4,100,000. Fractional gastric analysis with histamine revealed no free hydrochloric acid.

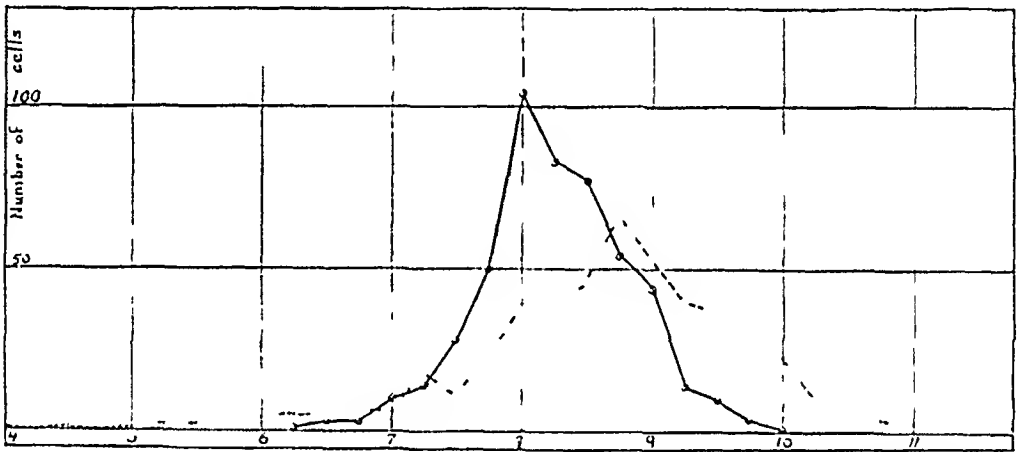


Chart 19 (case 9) —Price-Jones curves, each of 500 cells. On March 27, 1930 (dotted line), erythrocytes were 1,160,000 and hemoglobin 34 per cent, on May 19 (circles), erythrocytes 3,560,000 and hemoglobin 95 per cent.

CASE 10—Z. T., a woman aged 56, complained of tiredness and loss of energy for two years. Six months before examination, her condition became much worse, she looked pale and complained of palpitation and pain in the chest on the least exertion. She also complained of pain in the tongue and tingling and numbness in the hands and feet, she did not have diarrhea.

On examination, the skin was pale and yellowish, the conjunctivae were anemic and the sclerae slightly jaundiced. The teeth were in a poor condition and the tongue was smooth. The area of cardiac dullness showed a slight increase to the left, systolic murmurs were heard at the various ostia.

The urine contained a trace of albumin, tests for urobilin were strongly positive. Examination of the blood showed hemoglobin, 32 per cent, erythrocytes, 1,350,000, color index, 1.1, white blood cells, 3,700, reticulocytes, 25 per thousand, marked anisocytosis and poikilocytosis, polychromatophilia and punctate basophilia, 6 normoblasts and 2 megaloblasts in 100 white cells, blood platelets definitely diminished. The direct van den Bergh test yielded negative results, the indirect test gave 16 mg of bilirubin per liter of serum. The Wassermann and Sachs-Georgi tests were negative. The feces contained no blood. Fractional

gastric analysis revealed no free hydrochloric acid, the highest total acidity was 27

A spoonful of stomach extract was given six times a day. The maximum reticulocytosis was reached about ten days after the treatment was begun, after thirty days' treatment, cytologic examination showed hemoglobin, 80 per cent,

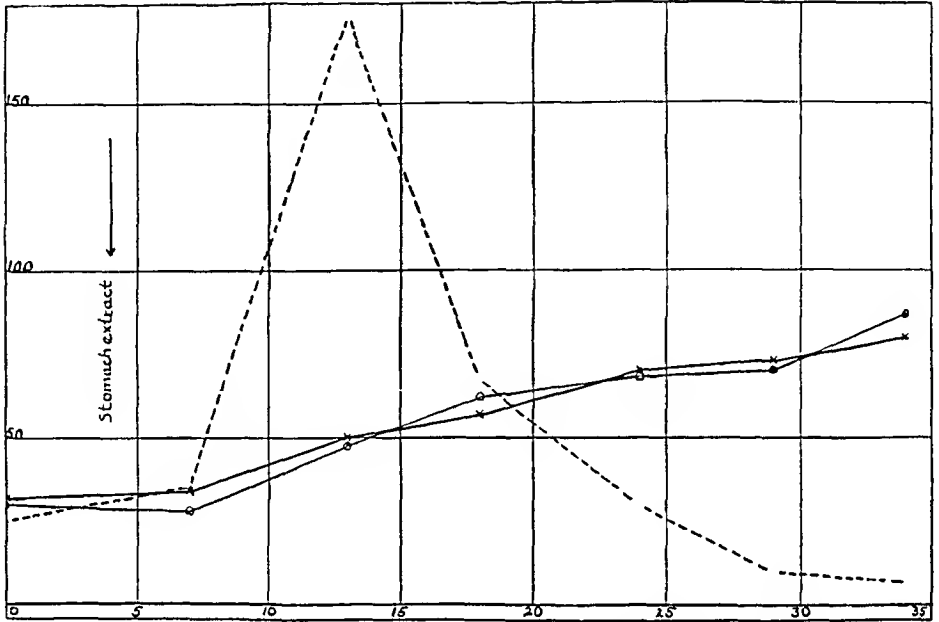


Chart 20 (case 10) —Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line)

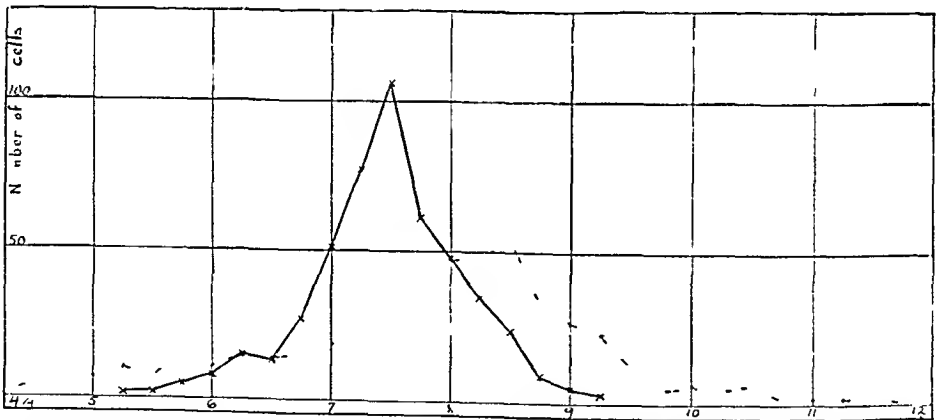


Chart 21 (case 10) —Price-Jones curves, each of 500 cells. On April 25, 1930 (dotted line), erythrocytes were 1,350,000 and hemoglobin 32 per cent, on May 30 (crosses), erythrocytes 3,910,000 and hemoglobin 80 per cent

and erythrocytes, 3,910,000. The Price-Jones curves (chart 21) show a remarkable improvement in the megalocytosis.

CASE 11—M S, a woman, aged 71, was well until fourteen months before examination, when she began to complain of lassitude and loss of energy. She was then treated with liver and remained well for seven months, then she was again

given liver, but unsuccessfully. She was discharged from the hospital in forty days with a hemoglobin percentage of only 34. Since then she had been bedridden.

On examination, the skin was a lemon-yellow color, no cyanosis or dyspnea was present. The conjunctivae were extremely anemic. The teeth were in a poor condition, the tongue was smooth and atrophic. The area of cardiac dulness was

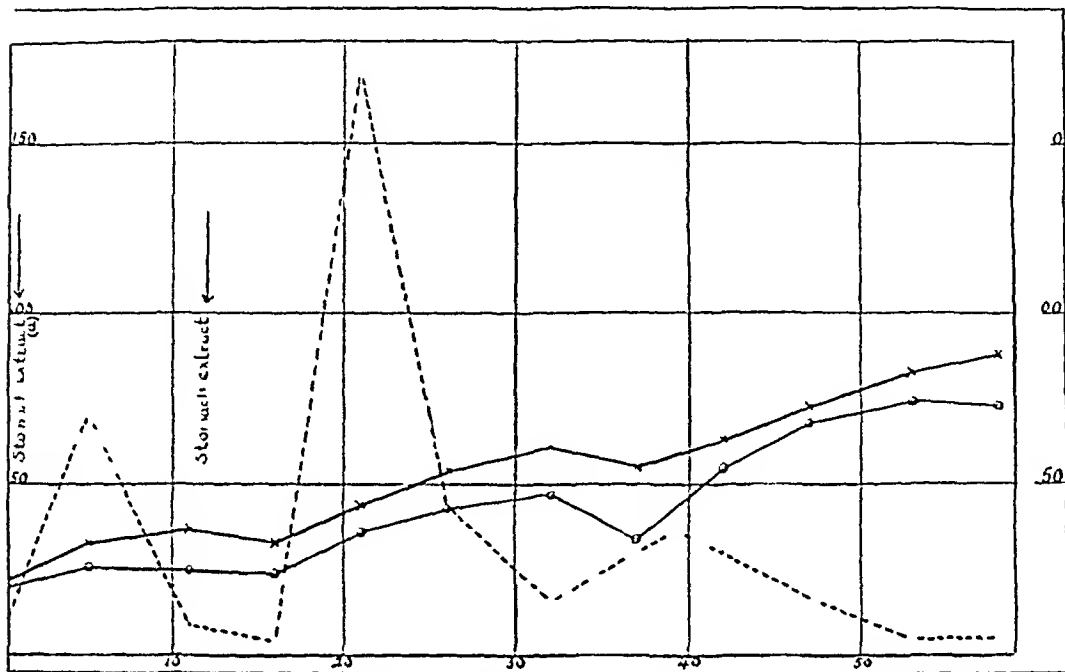


Chart 22 (case 11) —Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line)

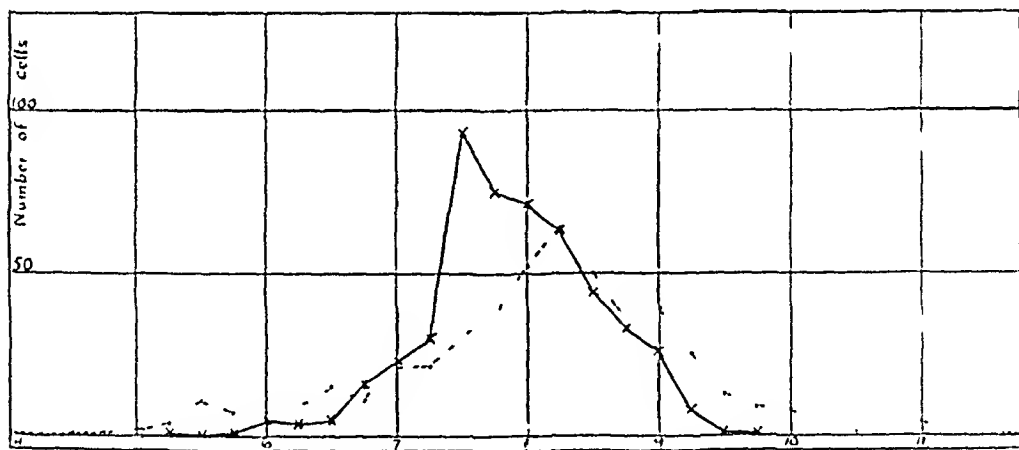


Chart 23 (case 11) —Price-Jones curves, each of 500 cells. On April 3, 1930 (dotted line), erythrocytes were 900,000 and hemoglobin 22 per cent, on May 31 (crosses), erythrocytes 3,260,000 and hemoglobin 88 per cent.

normal, systolic murmurs were heard at all ostia. Râles were heard over the left lower lung posteriorly. The liver and spleen were not palpable.

The urine contained a trace of albumin, tests for urobilin gave strongly positive results. Examination of the blood showed hemoglobin, 22 per cent, erythrocytes, 900,000, color index, 1.1, leukocytes, 3,400, reticulocytes, 10 per thousand,

marked poikilocytosis and anisocytosis, polychromatophilia and punctate basophilia, 2 megaloblasts and several normoblasts in 100 white cells, a few blood platelets. The direct van den Bergh test gave negative results, the indirect test yielded 22 mg of bilirubin per liter of serum. The Wassermann and Sachs-Georgi tests of the blood gave negative results. The feces contained no blood. Fractional gastric analysis revealed no free hydrochloric acid.

A German preparation of desiccated hog's stomach was given, 2 tablets four times a day. There was a slight reticulocytosis on about the fifth day, but as there was no general improvement, the German preparation was replaced by the stomach extract used in the previous cases, a tablespoonful a day, with the gratifying result that ten days later, the reticulocytosis reached a much higher level (172 per thousand). From then on there was a steady general improvement, at the end of fifty days' treatment with the second stomach extract the hemoglobin was 88 per cent and the erythrocytes were 3,260,000.

This was a great success for the stomach therapy. The condition of the patient was extremely poor and the prognosis doubtful considering her age, the hypostasis of the lungs, the extreme emaciation and the fact that liver therapy had been unsuccessful on a prior occasion.

COMMENT

It is interesting to note that the return of the red blood cells to normal size generally lagged behind the improvement in the percentage of hemoglobin, the red blood count, etc. In cases 2 and 3 it was possible to measure the diameters of the red blood cells five and four months, respectively, after the patient's discharge from the hospital, and it was found that the morphologic recovery had become complete. Minot and Medearis⁵ studied the diameter of the red blood cells in patients treated with liver and came to a somewhat similar conclusion.

Since the beginning of these experiments and after our provisional report⁶ of the first five cases, several workers have published their experiences on this subject. Wilkinson,⁷ in England, successfully treated four patients with raw hog's stomach and two patients with desiccated stomach. He also showed that both the muscularis and the mucosa are active. Renshaw⁸ in the same country, succeeded with this treatment in a case that had proved refractory to liver. Hitzemberger,⁹ of Vienna reported one case and Rosenow,¹⁰ of Berlin, two cases, in which treatment with desiccated hog's stomach was successful. Recently Meulengracht and Hecht-Johansen,¹¹ of Copenhagen, reported four

5 Minot and Medearis. *J Clin Investigation* **3** 541 (Feb 20) 1927.

6 Snapper, I, and du Preez, J. D. G. *Nederl tijdschr v geneesk* **74** 745 (Feb 15) 1930.

7 Wilkinson. *Brit M J* **1** 236 (Feb 8) 1930.

8 Renshaw. *Brit M J* **1** 334 (Feb 22) 1930.

9 Hitzemberger. *Wien klin Wchnschr* **43** 367, 1930.

10 Rosenow. *Klin Wchnschr* **9** 652 (April 5) 1930.

11 Meulengracht and Hecht-Johansen. *Klin Wchnschr* **9** 1162 (June 21) 1930.

cases in which pulverized desiccated hog's stomach, and two cases in which a stomach extract, was used

Treatment for pernicious anemia with hog's stomach has theretofore been established beyond all doubt. The consequences must be great, both theoretically and practically. Cases refractory to treatment with liver, especially with liver extracts, are not rare, besides, hog's stomach is a cheap article and, if equally active as a blood-maturing agent, will supersede the more expensive liver preparations and so bring a good and effective treatment within the reach of the general public.

CARBOHYDRATE METABOLISM IN HYPERTENSION *

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AND

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BROOKLYN

It has been noted by clinical observers that a disturbance of carbohydrate metabolism exists in hypertension

In 1910, Neubauer¹ observed the association of hyperglycemia in nephritis with hypertension, and postulated that an overactivity of the suprarenal glands was the causative factor. Hagelberg² made the same observation and accepted Neubauer's theory. Tachau³ also concurred in these observations, but did not attempt to explain the mechanism involved. Bing and Jakobsen⁴ were of the opinion that the hyperglycemia in all cases of hypertension with nephritis could be explained by a complicating condition such as dyspnea, uremia or a cerebral accident.

Hopkins⁵ also observed hyperglycemia in hypertension with nephritis. Hamman and Hirschman⁶ found that cases of high blood pressure, especially when complicated by nephritis, showed a so-called 'diabetic' blood sugar curve after the administration of dextrose. Hirsch⁷ noted that in the majority of cases of vascular hypertension without nephritis there was hyperglycemia and an abnormal rise in blood sugar after the taking of dextrose. Herrick⁸ concurred in the opinion that high blood

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1 Neubauer, E. Ueber Hyperglykämie bei Hochdrucknephritis, *Biochem Ztschr* **25** 284, 1910

2 Hagelberg, M. Hypertonie und Blutzucker, *Berl klin Wchnschr* **40** 1877, 1912

3 Tachau, H. Eine neue Methode der Bestimmung des Blutzuckergehaltes, *Deutsches Arch f klin Med* **102** 597, 1911

4 Bing, H J, and Jakobsen, B. Blutzucker Untersuchungen unter normalen und einigen pathologischen Verhältnissen, *Deutsches Arch f klin Med* **113** 571, 1913

5 Hopkins, A H. Studies in Concentration of Blood Sugar in Health and Disease, *Am J M Sc* **149** 254, 1915

6 Hamman, L, and Hirschman, I I. Studies on Blood Sugar, *Arch Int Med* **20** 761 (Nov) 1917

7 Hirsch, E. Blutzucker und vasculare Hypertonie, *Biochem Ztschr* **75** 189, 1916

8 Herrick, W W. Hypertension and Hyperglycemia, *J A M A* **81** 1942 (Dec 8) 1923

sugar occurred in cases of high blood pressure, more often when it was not associated with obvious disease of the kidney

Kahler⁹ found hyperglycemia in essential hypertension and believed that the possibility of the existence of sclerosis of the pancreatic blood vessels should be considered. Fahr¹⁰ also postulated that the high blood sugar in cases of high blood pressure might be the result of a diminution in the output of insulin engendered by a sclerosis of the blood vessels of the pancreas. O'Hare¹¹ observed that a large number of cases of hypertension showed a high blood sugar curve after the ingestion of dextrose and he believed that many of the patients were potentially diabetic.

Hitzenberger and Richter-Quittner¹² revived the theory of Neubauer. They stated that in both primary and secondary hypertension, hyperglycemia and elevation of the renal threshold for dextrose were present. The condition of hyperglycemia, hypertension and elevation of the renal threshold can be produced by the injection of epinephrine. Therefore they urged that the entire complex could be explained by an increase in secretion by the suprarenals.

Only two observers reported contradictory observations. Knoopman¹³ found high blood sugar in hypertension to be exceptional. Iwai and Lowy¹⁴ noted that the blood sugar level during fasting and the blood sugar curve after the ingestion of dextrose were essentially normal in cases of high blood pressure.

Of interest in relation to this subject are the observations of Punschel¹⁵ and of Spence¹⁶. They observed that in senility the blood sugar value during fasting and the dextrose tolerance curve were much higher than in young people.

It seems to be fairly definitely established, then, that in hypertension, whether or not complications such as nephritis exist, there is a

9 Kahler, H. Zur Pathogenese der essentiellen Hypertonie, Wien Arch f inn Med **3** 129, 1922

10 Fahr, G. Kurzer Beitrag zur Frage der Hypertonie, Berl klin Wchnschr **58** 730, 1921

11 O'Hare, J. P. Glucose Tolerance Test in Chronic Vascular Hypertension, Am J M Sc **160** 366, 1920

12 Hitzenberger, K., and Richter-Quittner, M. Ein Beitrag zum Stoffwechsel bei der vaskularen Hypertonie, Wien Arch f inn Med **2** 189, 1921

13 Knoopman, J. Blood Pressure and Sugar Metabolism, Endocrinology **8** 340, 1924

14 Iwai, S., and Lowy, F. E. Zur Frage der Hyperglykämie bei Hochdruck, Klin Wchnschr **3** 1440, 1924

15 Punschel, A. Der Blutzucker im höheren Lebensalter unter besonderer Berücksichtigung der alimentären Hyperglykämie, Ztschr f klin Med **96** 253, 1923

16 Spence, J. C. Some Observations on Sugar Tolerance with Special Reference to Variation Found at Different Ages, Quart J Med **14** 314, 1920-1921

disturbance in the metabolism of carbohydrate. This may manifest itself as hyperglycemia and glycosuria. The more constant feature, however, is the exhibition of a high blood sugar curve on the administration of an adequate amount of dextrose.

The elucidation of the factors concerned in this disturbance is not simple. Fahl,¹⁰ Kahlei,⁹ and O'Hare¹¹ considered this condition to be the result of a diminution in the secretion of insulin engendered by sclerosis of the blood vessels of the pancreas, or, to put it more concretely, these cases are either potentially or mildly diabetic. Neubauer,¹ Hagelbeig,² Tachau,³ and Hitzengerber and Richter-Quittner,¹² on the other hand, expressed the belief that the entire picture can be explained by the existence of a hyperadrenalemia.

The differences between these two conceptions are fundamental. In both conditions a "diabetic" blood sugar curve is obtained on the administration of dextrose. In diabetes mellitus the respiratory quotient curve is lower than normal after the ingestion of dextrose, in hypersuprarenalemia, on the other hand, the curve is normal. This point is of cardinal importance because it helps separate diabetic from nondiabetic patients. Thus Linder, Hillel and Van Slyke¹⁷ found that in nephritis, in which there may be a marked diminution in tolerance for dextrose, the respiratory quotient curve is normal. Similarly, Sanger and Hun¹⁸ found this to be true in hyperthyroidism. We¹⁹ suggested that a study of the respiratory quotient curve would serve to distinguish diabetic from nondiabetic cases in acromegaly, in which there is practically always a disturbance in carbohydrate metabolism.

At this point a few words may be said about the respiratory quotient curve. The respiratory quotient of normal persons twelve hours after a meal was determined by Benedict, Emmes, Roth and Smith²⁰ and found to be 0.83 for men and 0.81 for women. As a rule it is lower in diabetic patients, the more severe the diabetes, the lower is the quotient. The respiratory quotient during fasting will be lower in normal persons if they have been deprived of carbohydrates for several days. Conversely, it has been shown by Benedict, Emmes and Riche²¹ that following an evening meal rich in carbohydrate, the respiratory quotient on

17 Linder, G. C., Hillel, A., and Van Slyke, D. D. Carbohydrate Metabolism in Nephritis, *J. Clin. Investigation* **1** 247, 1925.

18 Sanger, B. J., and Hun, E. G. The Glucose Mobilization Rate in Hyperthyroidism, *Arch. Int. Med.* **30** 397 (Sept.) 1922.

19 Wishnofsky, M., and Byron, C. S. Carbohydrate Metabolism in Acromegaly, *J. Lab. & Clin. Med.* **15** 216, 1929.

20 Benedict, F. G., Emmes, L. E., Roth, P., and Smith, H. M. The Basal, Gaseous Metabolism of Normal Men and Women, *J. Biol. Chem.* **18** 139, 1914.

21 Benedict, F. G., Emmes, L. E., and Riche, J. A. The Influence of the Preceding Diet on the Respiratory Quotient After Active Digestion Has Ceased, *Am. J. Physiol.* **27** 383, 1911.

the following morning may be 0.88. It is seldom, however, that such marked changes in the diet are encountered as were employed by these experimenters with their subjects.

It has been shown by Bernstein and Falta²² and others that after the administration of dextrose the respiratory quotient will not rise until an optimum percentage of glycogen is obtained in the liver. It is only after the glycogen depots have been filled that the oxidation of dextrose will commence. Consequently, in a person who has been on a diet poor in carbohydrate for several days, there will be a delay in the rise of the respiratory quotient, whereas when the body is supplied with glycogen there will be an early rise which to some extent must be attributed to the conversion of carbohydrate into fat. Gigon²³ found that in a normal person the respiratory quotient never rises before one-half hour after the administration of dextrose. Indeed, Bornstein and Holm²⁴ found that it may actually fall during the first fifteen minutes, and they suggested that this may be due to carbon dioxide being retained in the body to combine with the alkali released by the secretion of acid in the gastric juice. The respiratory quotient is highest at the end of three hours, at which time the blood sugar is normal. The quotient during fasting is, as a rule, attained at the end of from four to six hours.

Ten cases of hypertension were investigated by us along these lines, namely, by a simultaneous study of the blood sugar and the respiratory quotient curves. These cases were chosen at random from the outpatient department. The ages of the patients ranged from 40 to 70 years. The lowest systolic blood pressure was 170 mm. of mercury, in most cases it was considerably above this. The patients were on normal diets previous to the day of the test. This point is of extreme importance, for, as mentioned, if the person is on a diet poor in carbohydrate for several days, an abnormally low curve for the respiratory quotient will result on the administration of dextrose. It has also been demonstrated that under similar conditions a "diabetic" blood sugar curve can be obtained in normal persons.

The question of standards of normal will now be considered. A normal blood sugar curve (venous blood) may be accepted as one that has a fasting level of from 0.8 to 0.11 per cent, that reaches its peak in one hour—as a rule much earlier—after the ingestion of dextrose, rarely going higher than 0.17 per cent, and that tends to regain its fasting level and frequently even a lower value within two hours, and occasionally in three hours. In two cases blood from the tips of the

22 Bernstein, S., and Falta, W. Respiratorischer Stoffwechsel und Blutzucker Regulation, *Deutsches Arch f klin Med* **125** 233, 1918.

23 Gigon, quoted by Bornstein and Holm. *Biochem Ztschr* **130** 210, 1922.

24 Bornstein, A., and Holm, K. Ueber den respiratorischen Stoffwechsel bei alimentarer Glykämie, *Biochem Ztschr* **130** 209, 1922.

finger was utilized, which has been shown by Foster²⁵ to be identical with that of arterial blood. For reasons that need not be discussed here, when arterial blood is used the blood sugar curve is higher than that for venous blood. According to Foster²⁵ and from our own experience, the figures of a normal blood sugar curve (arterial blood) are as follows: 0.10 per cent fasting level, and 0.21 and 0.12 per cent, three quarters of an hour and two hours after the ingestion of dextrose, respectively.

The respiratory quotient curves of Sanger and Hun¹⁸ were accepted as standards of normal (table 1). Their normal subjects received 1.75 Gm of dextrose per kilogram of body weight, which is the amount given to our patients with hypertension. Their figures are substantiated by the work of Boinstein and Holm²¹.

METHOD OF PROCEDURE

After having fasted for fourteen hours, each patient received 1.75 Gm of dextrose per kilogram of body weight. Three specimens of blood were taken

TABLE 1—*Curves of Respiratory Quotient in Normal Controls*
(Sanger and Hun)

Name	Basal	30 Minutes*	60 Minutes	90 Minutes	120 Minutes	150 Minutes	Range
O. L.	0.78	0.82	0.80	0.89	0.87	0.94	0.16
H. D.	0.83	0.81	0.80	0.88	0.88	0.90	0.09
W. U. G.	0.75	0.84	0.88	0.88	0.84	0.90	0.15
E. H.	0.77	0.80	0.80	0.90	0.92	0.90	0.15
B. S.	0.78	0.80	0.84	0.86	0.88	0.86	0.10
M. C.	0.79	0.82	0.88	0.89	0.92	0.93	0.14
M. C.	0.83	0.83	0.86	0.83	0.92	0.90	0.09
H. J.	0.85	0.83	0.84	0.88	0.93	0.89	0.10
R. Mc.	0.83	0.88	0.84	0.88	0.93	0.92	0.10
H. R. Q.	0.75	0.79	0.81	0.86	0.83	0.87	0.12
Average	0.80						0.12

* 1.75 Gm of dextrose per kilogram of body weight.

from each patient, one at the "fasting level," and two forty-five minutes and two hours after ingestion, respectively. The sugar content of the venous blood was determined by the Folin-Wu method, and that from the tip of the finger by the Kramer-Gittleman²⁶ micromethod. The respiratory quotient was determined at the "fasting level," and at one and one-fourth and at two and one-fourth hours after ingestion, respectively. These time intervals were chosen after careful consideration as best describing the nature of the curve. The gas was collected in a Tissot spirometer and analyzed by the method of Henderson and Haldane.

RESULTS

The results are incorporated in table 2. The blood sugar curves will be examined first. Accepting 0.11 per cent as the upper limit of normal, six of the ten patients had blood sugar values during fasting above normal. The ten patients had blood sugar curves above normal.

25 Foster, G. L. Some Comparisons of Blood Sugar Concentrations in Venous Blood and in Finger Blood, *J. Biol. Chem.* **55** 291, 1923.

26 Kramer, B., and Gittleman, I. F. Technic for Quantitative Estimation of Sugar in Very Small Amounts of Blood, *J. A. M. A.* **81** 1171 (Oct. 6) 1923.

TABLE 2—Curves for Blood Sugar and Respiratory Quotient in Cases of Hypertension

	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6		Case 7		Case 8		Case 9*		Case 10*	
	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient
Fasting level	118	0.73	91	0.75	102	0.80	115	0.70	111	0.79	133	0.75	96	0.72	81		151	0.81	148	0.79
45 minutes†	214		172		157		166		214		205		183		172		260		236	
75 minutes		0.83		0.89		0.88		0.88		0.92		0.856		0.83		0.89		0.92		0.88
120 minutes	100		145		191		191		172		187		140		138		210		214	
135 minutes		0.91		0.90		0.89		0.87		0.96		0.845		0.92		0.91		0.88		0.89

* In cases 9 and 10 blood was taken from the tip of the finger

† The patients were given 1.75 Gm of dextrose per kilogram of body weight

After careful consideration of the figures of Sanger and Hun¹⁸ and those of Bornstein and Holm,¹ it was decided that the respiratory quotient curve may be considered normal if its peak is 0.88 or more after the ingestion of 1.75 Gm. of dextrose per kilogram of body weight. According to this standard, all of the patients, except the one in case 6, had normal respiratory quotient curves. In case 6 the quotient rose only to 0.856. This patient also had the highest value for blood sugar during fasting, 0.133 per cent.

COMMENT

In diabetes mellitus there is a deficiency in glycogenesis and storage of glycogen. Whether or not there is also a diminution in the ability to oxidize dextrose is still in a polemic state. Macleod²⁷ stated, "The occurrence of these low quotients and their failure to respond to ingestion of glucose are often cited as evidence that the tissues in diabetes have lost the power to oxidize carbohydrate, but there is no direct evidence that this is really so." Joslin²⁸ expressed the belief that the diabetic patient can burn sugar if the sugar can first be transformed into glycogen. This may be accepted as incontrovertible that in diabetes the respiratory quotient during fasting is lower than normal, and that the respiratory quotient curve fails to rise to a normal level after the ingestion of dextrose. A low curve for the respiratory quotient indicates a deficiency of insulin or a neutralization or inactivation of an adequate supply of insulin.²⁹ The converse is true, namely, that a normal respiratory quotient indicates an adequate secretion of insulin.

A large amount of work has been done on the use of the dextrose tolerance test in the diagnosis of diabetes mellitus. However, a so-called 'diabetic curve' is obtained in so many conditions that this test must be considered inadequate. Far more information may be obtained by studying simultaneously the blood sugar and the respiratory quotient curves.

The various theories advanced to explain the disturbance in carbohydrate metabolism in hypertension will now be reconsidered. They are (1) the existence of sclerosis of the blood vessels of the pancreas leading to a diminution in the secretion of insulin, and (2) the presence of a hyperadrenalemia.

27 Macleod, J. J. R. *Physiology and Biochemistry in Modern Medicine*, ed. 6, St. Louis, C. V. Mosby Company, 1930, p. 912.

28 Joslin, E. P. *The Treatment of Diabetes Mellitus*, ed. 4, Philadelphia, Lea & Febiger, 1928, p. 103.

29 This does not include phlorizin diabetes, in which the respiratory quotient rises only slightly after the administration of dextrose. This is the result, not of the inability of the organism to oxidize dextrose, but of the rapid elimination of dextrose by the kidney.

In nine of ten cases examined by us the respiratory quotient curve was normal after the ingestion of dextrose. This is definite evidence that there is an adequate secretion of insulin, that is, that diabetes mellitus does not exist. In the single case in which the respiratory quotient curve was lower than normal, the diagnosis of diabetes mellitus could be made, which condition is coexistent with and independent of the hypertension.

The injection of epinephrine gives rise to a "diabetic" blood sugar curve after the ingestion of dextrose. It was shown by Lusk³⁰ that if dextrose was given to normal dogs and then epinephrine was administered the respiratory quotient rose to unity, showing a normal combustion of carbohydrate. A hyperadrenalemia could then give rise to blood sugar and respiratory quotient curves as found by us.

In 1904, Vaquez³¹ formulated the doctrine that hypertension is due to a hyperadrenalemia. Janeway³² characterized this as a "beautiful dream." Broking and Trendelenburg³³ did not find an increase of epinephrine in the blood in hypertension. Stewart³⁴ stated that it is impossible to demonstrate epinephrine in human serum. It might be added that hyperplasia and adenoma of the suprarenal cortex are common in hypertension, but it is the medulla which secretes epinephrine, and changes are rarely found there.

In the present state of knowledge the theory that hyperadrenalemia causes the disturbance in carbohydrate metabolism cannot be proved.

When one considers the fact that in diabetes mellitus the explanation of the pathologic physiology is still in the stage of "theories," it is not strange that we should be in the dark about the mechanism concerned in the disturbance of carbohydrate metabolism in hypertension. Our object in performing this work was twofold: (1) to confirm that a disturbance of carbohydrate metabolism does exist, and (2) to determine its relation to diabetes mellitus. From our observations it can be deduced that a disturbance exists in all cases of hypertension that are not related to diabetes. Much more research of carbohydrate metabolism in general is necessary before we can hope to explain the pathologic physiology of this condition.

30 Lusk, G. The Alleged Influence of the Adrenals on Diabetic Metabolism, *Arch Int Med* **13** 673 (May) 1914.

31 Vaquez, quoted by Oppenheimer, B. S., and Fishberg, A. M. Association of Hypertension with Suprarenal Tumors, *Arch Int Med* **34** 631 (Nov.) 1924.

32 Janeway, T. C. Nephritic Hypertension, *Am J M Sc* **145** 638, 1913.

33 Broking, E., and Trendelenburg, P. Adrenalin-nachweis und Adrenalin-gehalt des menschlichen Blutes, *Deutsches Arch f klin Med* **103** 163, 1911.

34 Stewart, G. N. So-Called Biological Tests for Adrenalin in Blood, with Some Observations on Arterial Hypertonus, *J Exper Med* **14** 377, 1911.

SUMMARY AND CONCLUSIONS

A dextrose tolerance test was performed on ten patients suffering from hypertension. The blood sugar and the respiratory quotient curves were studied simultaneously. In six of the ten cases the blood sugar during fasting was higher than normal. It was shown that all patients with hypertension have high blood sugar curves. The respiratory quotient curves were normal in nine of the ten cases. This is adequate proof that there is no diminution in the secretion of insulin in hypertension, and that these patients are neither potentially nor mildly diabetic. It disproves the theory that the disturbance in carbohydrate metabolism in hypertension is caused by sclerosis of the blood vessels of the pancreas. In the case in which the respiratory quotient curve was lower than normal, diabetes mellitus, independent of the hypertension, could be considered to exist.

The theory that hyperadrenalemia is the cause of the disturbance cannot be proved in the present state of knowledge.

The mechanism concerned in producing this disturbance in carbohydrate metabolism in hypertension is unknown and awaits further research for its elucidation.

PROGRESSIVE THROMBOSIS OF THE PULMONARY ARTERY¹

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AND

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Although the fatal pulmonary thromboses usually follow major operations or are postoperative, yet purely medical thrombi do occur, and in the artery the latter are more frequently primary than embolic. The facts that the pulmonary artery functions as a vein and that the blood it conveys is more venous than that in any other vein lead it to the same thrombotic accidents to which veins elsewhere are subjected. Sepsis, anesthesia, athromatous changes, stasis in the blood stream and low blood pressure all predispose to the formation of a thrombus, and the case reported here illustrates, we believe, such a combination of etiologic factors.

REPORT OF CASE

History—A shop foreman, aged 39, entered Rockford Hospital on Oct. 20, 1929, complaining of a general sense of uneasiness, malaise, anorexia, palpitation, shortness of breath, easy fatigue and some aching through the chest. He had always been a hard worker. Four weeks prior to admittance, he had experienced an acute respiratory infection, consisting of congestion in the head and a mild cough. This lasted three or four days, and the patient dated the foregoing symptoms from this time. Eight months prior to the present illness, he had an attack of pain on defecation with explosive stools containing some blood and mucus. There were two or three stools a day during this attack, which lasted three weeks. Belching and flatulence after heavy meals persisted, but the stools became well formed, normal in number and contained no blood or mucus.

The father died of a stroke at the age of 63. The mother was living and well.

Examination—The patient apparently was not seriously ill. The head, throat and neck were normal. The lungs were clear and resonant throughout, the cardiac rate was regular, and the heart was not enlarged, a soft systolic and diastolic murmur was heard at the apex.

There were no masses, tenderness or enlarged viscera in the abdomen. The lymph glands over the body were not enlarged, and the reflexes were normal. No foci of infection were found in the teeth, tonsils, sinuses or prostate.

Throughout the patient's stay in the hospital, his pulse rate ranged from 80 to 100, his temperature from 97 to 99 F., and his respiration from 20 to 30. The blood pressure was 108 systolic and 70 diastolic.

¹ Submitted for publication, Oct. 5, 1930.

² From the Departments of Internal Medicine and Pathology of Rockford Hospital.

A blood culture was sterile. The Kahn test was negative. The blood count revealed hemoglobin, 88 per cent, red blood cells, 4,300,000, white blood cells, 11,350, polymorphonuclears, 57 per cent, eosinophils, 1 per cent, basophils, 1 per cent, lymphocytes, 36 per cent, large mononuclears, 4 per cent. The red blood corpuscles were normal in size, shape and staining.

Chemical and microscopic examination of the urine gave negative results. No blood, pus, parasites or ova were found in the stool. A roentgenogram of the



Fig 1—Roentgenogram showing the thrombus in the pulmonary artery on the right side

chest showed increased density of the shadow of the right pulmonary artery, but its significance was not recognized before death.

Course.—After twenty-four hours in bed, the patient felt very comfortable, the pain in his chest and his general discomfort having subsided. On October 24, he was feeling better than at any time in the past two weeks. His heart was quiet, no murmurs or irregularities were heard, and there was no fever. As the blood culture was negative, the diagnosis of myocardial injury following the acute respiratory infection was thought probable.

On October 25, the patient had more dyspnea, the heart showed premature contractions, and a diastolic murmur returned.

On October 26, he had distress and gas in the upper part of the abdomen and passed a moderate amount of dark blood in the stool. This disappeared in twenty-four hours, and did not recur.

On October 29, after a good night's rest, the patient awoke and suddenly became dyspneic and cyanotic. This condition gradually progressed, his pulse became weaker, and he died late in the afternoon. He did not show the pallor of hemorrhage but cyanosis due to failure of the right side of the heart predominated.

Autopsy—The peritoneal, pleural and pericardial cavities were normal. The heart weighed 360 Gm. The right auricle was somewhat dilated. The cardiac



Fig 2—Print of the roentgenogram in figure 1 retouched to show the size and position of the thrombus.

muscle was reddish brown and firm, and the endocardium was smooth throughout. The valves were thin, delicate and smooth. The papillary muscles and chordae tendoneae were normal. The coronary vessels were pliable and not occluded. The aortic arch was not dilated. There was no gross atherosclerosis.

The muscle cells were not hypertrophied. There were some fragmentation, indistinct striation and vacuolization of fibers under the endocardium. Several sections through the coronary vessels were entirely normal.

The intima of the whole aorta was smooth, with no gross atherosclerosis.

The lungs crepitated, and the cut surface showed no solid areas except for about 1 cm. of the peripheral portion of the right lung, which was apparently

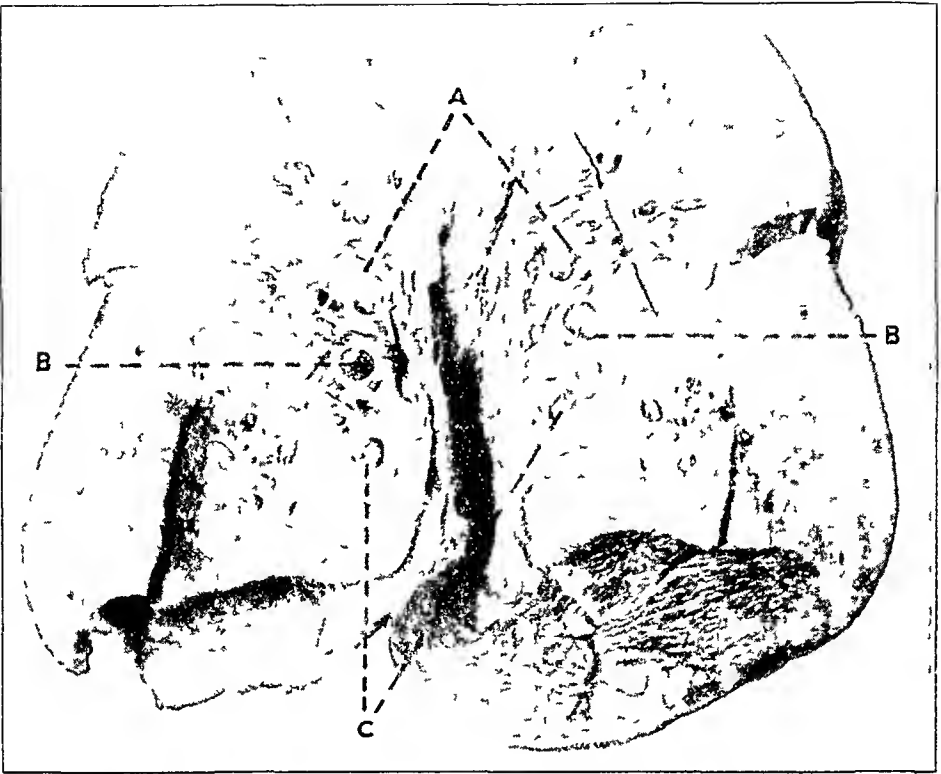


Fig 3—Photograph of the right lung sectioned through the hilus, showing the thrombi in the pulmonary artery and its branches *A* indicates the main artery, completely occluded Note that all but a small portion is an old thrombus Note the demarcation (*B*) between old and new parts of the thrombus The thrombus (*C*) here is old but does not completely occlude the vessel

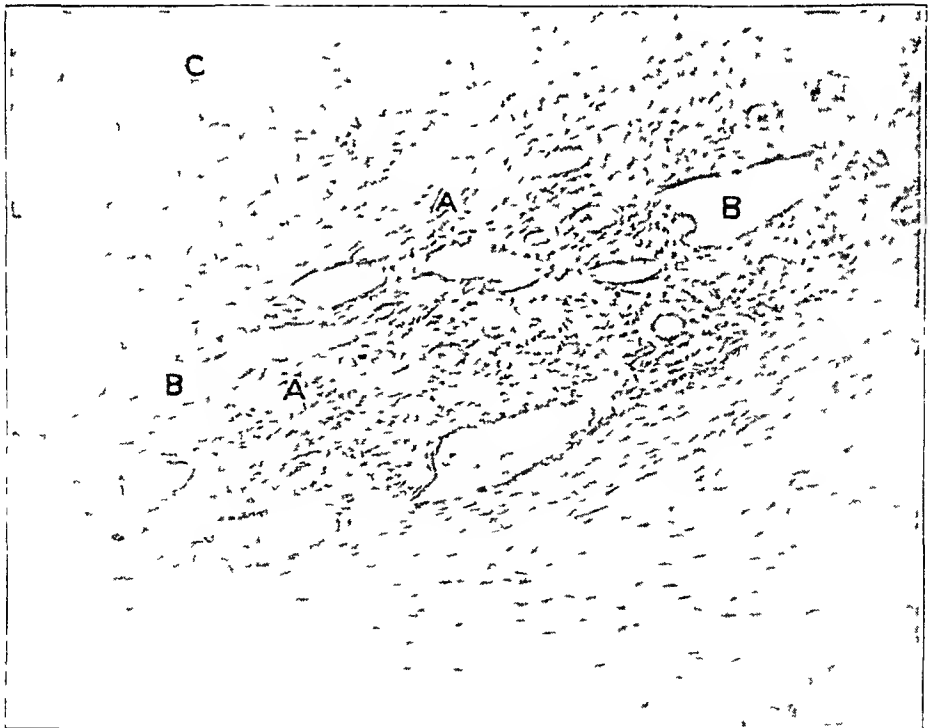


Fig 4—Photomicrograph through the wall of the pulmonary artery at the site of the older part of the thrombus Note organization (*A*), canalization (*B*) and lamellated clot (*C*)



Fig 5—High power photomicrograph of the wall of the pulmonary artery showing acute inflammation. Note the polymorphonuclears.

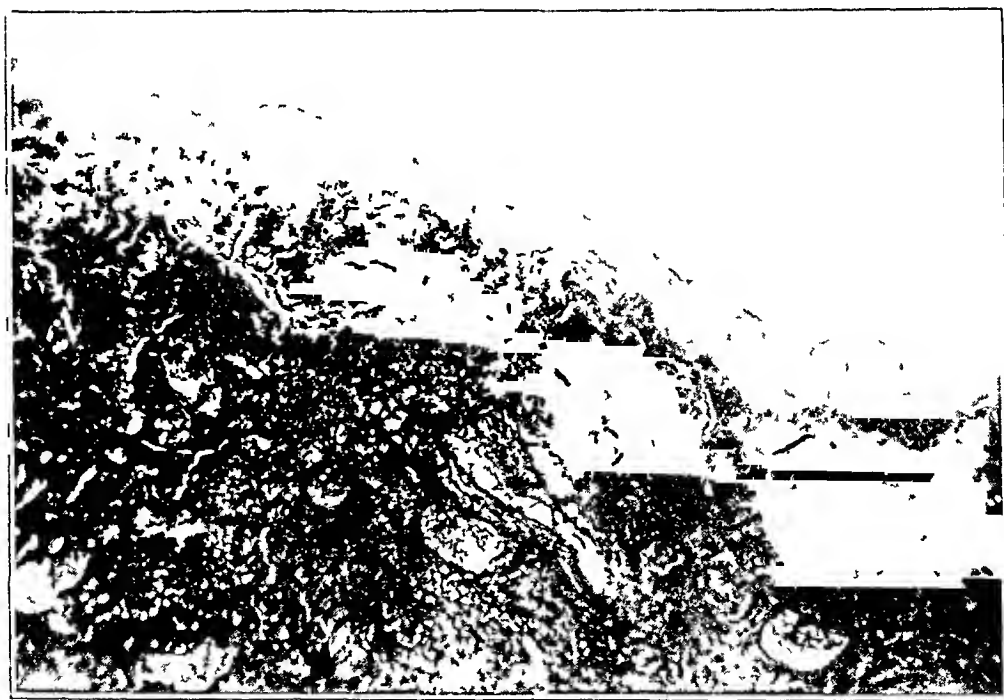


Fig 6—Photomicrograph of a section taken at the periphery of the right lung. This whole area is the seat of hemorrhagic infarction.

solid and very bloody. The lung from this portion to the hilus was spongy and quite normal, except that in the hilus one found the pulmonary artery completely filled with a thrombus. All of this thrombus, except a small portion at one extremity, was old, gray and firmly fixed around the whole periphery. The newer portion was red. Immediately adjacent was the bronchus, and numerous lymph glands lay beside the branches of the pulmonary artery. The thrombus extended into the ramification of the artery, but some of the branches were not completely occluded. The left lung showed a similar condition, except that most of the thrombus was new. It was, however, definitely fast to the wall.

A microscopic section at the periphery of the lung showed an area from 3 to 5 mm in depth (just beneath and including the pleural surface) to be the seat of recent hemorrhagic infarction. Sections through the pulmonary artery showed an old thrombus with advanced organization. The thrombus was firmly attached throughout nine tenths of its circumference. There was some canalization of the oldest portions. About one tenth of the thrombus was new.

The bronchus showed evidence of acute inflammation with polymorphonuclears very numerous just beneath the epithelium. The lymph glands were also chronically diseased, and there was a definite arteritis of the wall of the pulmonary artery where it was in contact with the lymph glands.

The liver, gastro-intestinal tract, spleen, supracrenals, kidneys, pelvic viscera and lymphatic structures were normal. The bone marrow, the organs of the neck, skull, sinuses and the spinal cord were not examined.

COMMENT

The patient had definite symptoms for some time prior to death, but these suddenly became aggravated and terminated fatally in a relatively short time. Postmortem examination revealed thrombo-arteritis of the pulmonary artery with complete occlusion. The thrombus was of some age, being well organized and in places canalized, though old the thrombus became complete only during the last few hours, as is shown positively by the newer portions of the thrombus. The thrombus on the left side was much less extensive, and probably the result of right-sided retrogression. There was no evidence of chronic congestion, showing that the heart was competent up to the time of the last sudden occlusion.

Had we been able to interpret the roentgen evidence properly, our diagnosis would have been simplified.

We believe this to be a case of thrombo-arteritis, primary in the pulmonary artery and not embolic. The sequence of events may have been (1) acute respiratory infection occurring five weeks before death resulting in (2) lymphadenitis and bronchitis, this infection extended into the pulmonary artery as an (3) arteritis. The high coagulability of the venous blood in the pulmonary artery accompanying the sepsis together with a low blood pressure slowing the stream over a damaged artery lining, produced (4) a thrombus which was not extensive enough to cause death at that time. Later, after a good night's rest, with slowing of the blood stream during sleep (5) another thrombus formed

and the symptoms appeared with the activity on awakening (6) Death did not occur until the new portion had retrogressed far enough to occlude the larger pulmonary branches

There was no attack of sudden pain, as is usual in cases of embolism, nor was any source for emboli found

Had this patient lived longer, the complete syndrome on which the diagnosis of Ayerza's disease could be made might have developed—hypertrophy of the right side of the heart from the extra work thrown on it, polycythemia, from the demand for more oxygen carriers, sclerosis of the pulmonary artery, chronic cough, cyanosis, and later serious cardiac failure

THE DYNAMICS OF THE CIRCULATION IN
COARCTATION (STENOSIS OF THE
ISTHMUS) OF THE AORTA
OF THE ADULT TYPE

RELATION TO ESSENTIAL HYPERTENSION *

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Coarctation of the aorta or stenosis of the aortic isthmus is of considerable interest, not only because of its rarity, but also because arterial hypertension is practically always present. Arterial hypertension exists above the level of the stenosis in this condition in the absence of renal lesions, arteriosclerosis or other complicating factors. The blood pressure below the level of the stenosis is much lower. Coarctation of the aorta, therefore, presents an unusual opportunity to compare in the same person the dynamics of the circulation in arterial hypertension as it exists above the coarctation with the dynamics of blood flow under lower pressure below the level of the stenosis.

Coarctation of the aorta has been diagnosed clinically in almost eighty patients, but no studies of the blood flow have hitherto been recorded. The purpose of this communication is to present the clinical observations in two patients with coarctation of the aorta, together with the oxygen capacity and content of the arterial and venous blood of the arms as compared to that of the legs, the tracings of the pulse of the carotid, brachial and femoral arteries, the blood pressure in the upper and lower extremities, the arteriolar pressure above and below the level of the stenosis, and measurements of the velocity of blood flow by the radioactive method above and below the coarctation of the aorta. The embryology, clinical observations, pathology and diagnostic

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criteria have been admirably reviewed by King,¹ Blackford,² Hamilton and Abbott,³ and Abbott,⁴ and will not be repeated here

REPORT OF CASES

CASE 1—History—D W, an unusually well developed white man, a teamster, aged 47, entered the hospital complaining of shortness of breath of four months' duration. The family and marital histories were irrelevant. Except for an acute left mastoiditis fifteen years previously, the patient had always felt well and had had no symptoms referable to the cardiovascular or other systems.

Five years previously, the patient had noted occasional cramps and increasing weakness of both legs. He had been able, nevertheless, to continue work as a teamster, lifting boxes that weighed from 150 to 200 pounds (68 to 90 Kg) many times every day. Four months before entry, he had symptoms of acute bronchitis, remained in bed three days, and then attempted to work. Shortness of breath became progressively more marked, particularly on lifting heavy boxes and on walking quickly. The cough also became worse, with paroxysmal exacerbations at night. Eleven weeks before admission to the hospital, he observed the onset of conspicuous palpitation of the heart, and was forced to use three pillows at night. Nine weeks before entry, he noticed a viselike pressure that was referable to the upper part of the sternum. This sensation of pressure was aggravated by exertion, but it did not radiate and was never associated with actual pain. He had not noticed edema at any time. In spite of these symptoms, he continued to work, but finally, eight weeks before admission to this hospital, he was so troubled by dyspnea and weakness that he was forced to enter the Boston City Hospital. At that time physical examination showed essentially the same findings as those noted later, except that the skin and sclerae were subicteric, signs of fluid were present over the base of the right side of the chest, and medium and coarse râles were heard elsewhere over the lungs. The signs of congestive failure gradually disappeared, and after four weeks, the patient was able to leave the hospital.

Physical Examination—Physical examination directly prior to our observations on June 3, 1929, showed an unusually well developed man. The pupils reacted normally. Ophthalmoscopic examination showed slight but definite arteriosclerosis of the retinal vessels. Heaving systolic pulsations of the carotid arteries were equally prominent in both sides of the neck. The right subclavian pulsation was greater than the left. No thrills were palpable over these vessels.

The thorax was symmetrical, normal in shape and expanded equally. Several tortuous, visibly pulsating vessels were noted over the back (fig 1). There were

1 King, J T, Jr. Stenosis of the Isthmus (Coarctation) of the Aorta and Its Diagnosis During Life, *Arch Int Med* **38** 69 (July) 1926

2 Blackford, L M. Coarctation of the Aorta, *Arch Int Med* **41** 702 (May) 1928

3 Hamilton, W F, and Abbott, M E. Coarctation of the Aorta of the Adult Type. I. Complete Obliteration of the Descending Arch at Insertion of the Ductus in a Boy of Fourteen, Bicuspid Aortic Valve, Impending Rupture of the Aorta, Cerebral Death, *Am Heart J* **3** 381, 1928

4 Abbott, M E. Coarctation of the Aorta of the Adult Type. II. A Statistical Study and Historical Retrospect of 200 Recorded Cases, with Autopsy, of Stenosis or Obliteration of the Descending Arch in Subjects Above the Age of Two Years, *Am Heart J* **3** 392, 1928

no thrills or murmurs over these vessels. The percussion note and breath sounds over both lungs were normal. No râles were heard. The apex impulse of the heart was normal and was felt in the fifth interspace 11 cm from the midsternal line. No thrills were present. Relative cardiac dulness extended 11 cm to the left and 4 cm to the right of the midsternal line. Supracardiac dulness measured 6 cm. A soft systolic murmur was heard over the mitral area, and a harsh systolic murmur was audible in the supraclavicular fossae, the axillae and over the great vessels of the neck, especially on the right. There were no diastolic murmurs, and there was no systolic murmur in the interscapular region. The

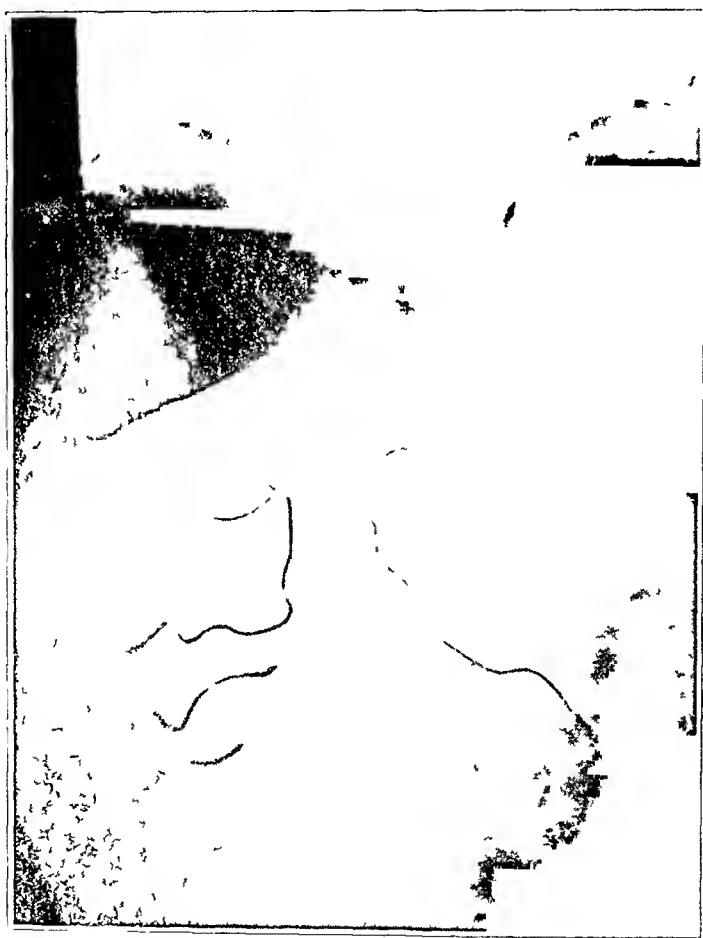


Fig 1 (case 1) —Posterior view showing the superficial vessels of the collateral circulation. The course of the dilated, pulsating arteries has been outlined with a skin-marking pencil. The pulsations in these vessels were obliterated by pressure laterally on the subscapular arteries. The flow of blood evidently was backward toward the aorta.

radial pulses were equal, synchronous, bounding in quality, and of high tension. The vessel walls were slightly tortuous and thickened. The femoral arterial pulsations were feeble, and the popliteal and posterior tibial pulsations were barely palpable. Pulsation of the dorsalis pedis arteries could not be felt. Examination of the legs gave otherwise negative results.

Examination of the abdomen revealed no abnormalities except for a few superficial, dilated, pulsating arteries in the upper part of the abdominal wall. Pulsa-

tion of the abdominal aorta could not be felt. Rectal examination revealed nothing abnormal. The temperature, respiratory rate and pulse rate were normal during the period of observation. The patient weighed 71.8 Kg, and was 166 cm in height.

Clinical Pathology—Repeated urinalyses gave negative results. The red blood cells numbered 5,260,000 per cubic millimeter, and there was 90 per cent hemoglobin as measured by the Sahli method. The white blood cells varied from 6,200 to 10,500 per cubic millimeter, and the various types of cells occurred in normal proportions. The Kahn reaction of the blood was negative. The non-protein nitrogen of the blood was 31 mg per hundred cubic centimeters. The phenolsulphonphthalein excretion was 35 per cent in two hours and ten minutes.

Electrocardiograms—Electrocardiographic tracings showed normal sinus rhythm, a rate of seventy per minute and left axis deviation. The duration of the



Fig 2 (case 1)—Roentgenogram of the chest, showing the erosion of the lower borders of the ribs on both sides. The scalloping extends forward approximately to the posterior axillary line.

Q R S complex was 0.12 seconds, that of the P-R interval was 0.18 seconds. The T wave was diphasic in all leads. The Q R S complexes in leads II and III were notched.

Roentgenograms—Roentgenographic films of the chest showed extensive irregularity of the inferior borders of the ribs posteriorly, extending forward approximately to the posterior axillary line (fig 2). This deformity probably was due to erosion by the pulsating, tortuous vessels of the collateral circulation.⁵ The cardiac measurements according to a roentgenogram taken at a distance of 7 feet (213 cm.)

⁵ Railsback, O. C., and Dock, W. Erosion of the Ribs Due to Stenosis of the Isthmus (Coarctation) of the Aorta, *Radiology* **12** 58, 1929.

were normal. Examination of the skull showed no definite evidence of cranial or intracranial abnormalities. Fluoroscopy of the chest by Dr Samuel A. Robins showed a moderate degree of emphysema. Forcible pulsations could be seen at the base of the heart and in the ascending portion of the aorta. These pulsations terminated in a narrow, triangular area situated posteriorly in the thoracic cavity at about the level of the angle of Ludwig. The descending portion of the aorta could not be made out definitely. The esophagus showed no abnormalities or transmitted pulsations.

Pulse Tracings—Tracings of the cardiac impulse and the carotid, radial and femoral pulse waves were recorded with a Sanborn-Mackenzie polygraph. The radial pulse wave occurred approximately 0.25 seconds after the cardiac impulse and approximately 0.15 seconds after the carotid pulse wave. These time relationships may be considered normal. The femoral pulse wave, instead of preceding the radial pulse wave by from 0.01 to 0.02 seconds as normally, followed the radial pulse wave by approximately 0.15 seconds (fig. 3). There was characteristic flat-

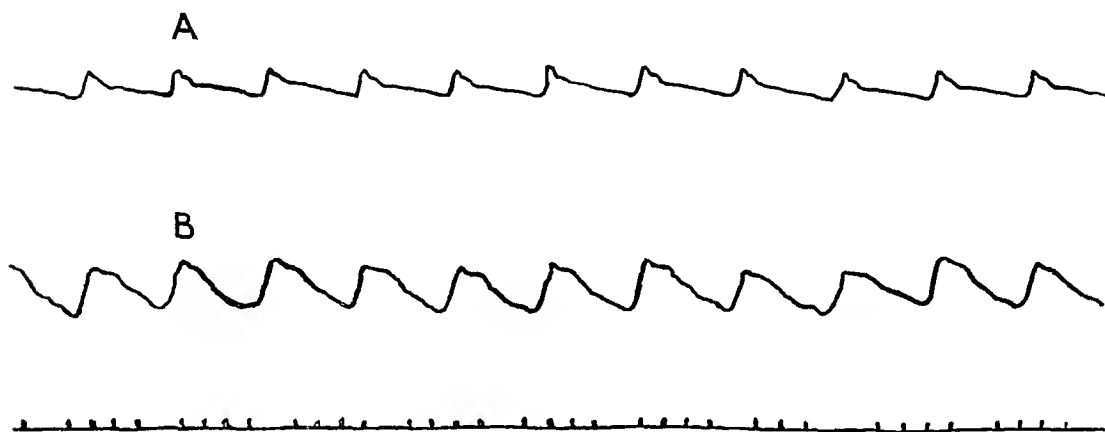


Fig. 3—Simultaneous tracing of the radial (a) and femoral (b) pulse waves. A correction of -0.15 seconds is necessary for the time of onset of the femoral wave because of the difference in the length of the lever arms of the apparatus at the levels recorded on the tape. The femoral pulse wave occurs 0.15 seconds after the radial pulse wave.

tening and prolongation of the femoral wave due to the circuitous path that the pulse followed in reaching the femoral arteries.

Blood Pressure Measurements—In the measurements of blood pressure, that of the right and left brachial arteries were equal and averaged 164 mm of mercury systolic and 94 mm of mercury diastolic. The standard mercury manometer with a cuff 14 cm in width was used.

A special cuff, 20 cm in width, was used in measuring the femoral blood pressure. The pressure was taken by auscultation over the popliteal artery with the cuff about the upper part of the thigh. The systolic pressure was 88 mm of mercury and the diastolic, 76 mm of mercury.

With a cuff about the calf of the leg and when the posterior tibial artery was palpated, the systolic pressure was 80.

Capillary and arteriolar pressures⁶ were measured according to the method used by Lewis and Haynal^{6a} and by Ellis and Weiss⁷. Open and closed capsules were used for the measurement of capillary pressure, and the closed capsule alone for arteriolar pressure. Over the sternum, the capillary pressure was 4 mm, and the arteriolar pressure 50 mm of mercury. Over the lateral aspect of the upper part of the arm, the arteriolar pressure was 50 mm, and over the lateral aspect of the upper part of the thigh, 45 mm of mercury.

Blood Volume Measurements—The volume of the blood and of the plasma were measured by the brilliant vital red dye method used by Thompson⁸. The dye was injected into the right antecubital vein, and the sample of blood was taken from the femoral vein. The results are shown in table 1.

Blood Gas Measurements—Duplicate measurements were made of the oxygen content and capacity of blood from the brachial artery, antecubital vein, femoral artery and femoral vein. The Van Slyke-Neill manometric apparatus⁹ was used. The results are presented in table 2.

TABLE 1—*Blood Volume Measurements in Case 1*

	Average Normal Values, Cc	Observed Values, Cc
Total plasma volume	3,550	3,460
Total blood volume	6,035	6,600
Plasma volume per kilogram	50	49
Blood volume per kilogram	85	93

6 By "capillary pressure" is meant the pressure necessary to cause minimal distinct blanching of the skin by compression of subpapillary venules.

By "arteriolar pressure" is meant the pressure transmitted to the subpapillary venules after dilatation of the arterioles and capillaries by histamine. The basis for believing that this pressure is due chiefly to arteriolar dilatation is presented by Lewis and Haynal. To what extent this pressure denotes the pressure in the "strongly muscled arterioles" cannot be stated since dilatation of the strongly muscled arterioles (the arched arterioles and the arterioles in the subpapillary network) and of the arterioles of the "minute vessels" (terminal arterioles) are important but indeterminate factors. Moreover, the degree to which these influences are opposed by capillary tone and frictional resistance cannot be stated precisely. As used in the present communication, the measurements of arteriolar pressure represent comparative values rather than quantitatively—precise measurements.

6a Lewis, T, and Haynal, I. Observations Relating to the Tone of the Minute Vessels of the Human Skin, with Remarks upon and Illustrations of Measurements of Pressure Within These Vessels, *Heart* **14** 177, 1928.

7 Ellis, L. B., and Weiss, S. The Measurement of Capillary Pressure under Natural Conditions and after Arteriolar Dilatation in Normal Subjects and in Patients with Arterial Hypertension and with Arteriosclerosis, *J Clin Investigation* **8** 47, 1929.

8 Thompson, W. O. Studies in Blood Volume. I. The Blood Volume in Myxedema with a Comparison of Plasma Volume Changes in Myxedema and Cardiac Edema, *J Clin Investigation* **2** 477, 1926.

9 Van Slyke, D. D., and Neill, J. M. The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J Biol Chem* **61** 523, 1924.

Blood Velocity Measurements—The velocity of blood flow of the lesser and greater circulations was measured by the radioactive method¹⁰ At the time these measurements were made, the pulse rate averaged 60 per minute, and was not significantly altered by the technical procedure The vital capacity of the lungs averaged 4.3 liters, or 2.4 liters per square meter of body surface, which is 96 per cent of the average for normal persons A summary of the measurements of the velocity of circulation is presented in table 3

CASE 2—History—T. M., a white man, aged 66, a retired freight handler, was referred to us through the courtesy of Dr. Henry A. Christian He was first admitted to the Peter Bent Brigham Hospital in February, 1918, complaining of shortness of breath on slight exertion, cough and palpitation of about five years duration These symptoms had become progressively worse during the preceding three weeks Physical examination revealed an enlarged heart with a blowing

TABLE 2—*The Utilization of Oxygen in Two Resting Subjects with Coarctation of the Aorta*

	Subject D. W.	Subject T. M.
Brachial artery		
Oxygen content, per cent by volume	17.73	16.07
Oxygen capacity, per cent by volume	19.64	17.86
Percentage saturation	90.3	89.9
Antecubital vein		
Oxygen content, per cent by volume	16.11	9.71
Oxygen capacity, per cent by volume	19.85	17.85
Percentage saturation	81.2	54.4
Ulnar artery		
Oxygen content, per cent by volume	17.74	
Oxygen capacity, per cent by volume	20.15	
Percentage saturation	87.2	
Ulnar vein		
Oxygen content, per cent by volume	13.85	5.51
Oxygen capacity, per cent by volume	19.77	17.97
Percentage saturation	70.1	31.4
Arteriovenous difference		
Aim, per cent by volume	1.62	6.26
Log, per cent by volume	3.89	10.56

systolic murmur over the entire precordium, auricular fibrillation, advanced generalized arteriosclerosis and the signs of infiltration of both apices Numerous fine and medium moist rales were heard everywhere over the chest, especially at the apices Tubercle bacilli were found in the sputum A large, tortuous artery was noted in the right side of the neck and a similar though smaller one in the left side The brachial blood pressure was 150 mm. of mercury systolic and 95 mm. of mercury diastolic The diagnosis was chronic tuberculosis of the lungs, enlargement of the heart, myocardial insufficiency, auricular fibrillation and generalized arteriosclerosis With rest in bed and the administration of digitalis, improvement was rapid at the end of three weeks the patient was transferred to the state sanatorium He remained there for eleven days and then decamped

¹⁰ Blumgart, H. L., and Yens, O. C. Studies on the Velocity of Blood Flow I. The Method Utilized, *J. Clin. Investigation* 4:1, 1927. Blumgart, H. L., and Weiss, S. Studies on the Velocity of Blood Flow VII. The Pulmonary Circulation Time in Normal Resting Individuals, *ibid.* 4:399, 1927. X. The Relation Between the Velocity of Blood Flow, the Venous Pressure and the Vital Capacity of the Lungs in Fifty Patients with Cardiovascular Disease Compared with Similar Measurements in Fifty Normal Persons *ibid.* 5:379, 1928.

From March, 1918, to January, 1930, the patient was admitted thirty times to the Peter Bent Brigham Hospital because of mild congestive heart failure and bronchitis that always subsided after a few weeks of treatment. In 1919, increased tortuosity and prominence of the subclavian and subscapular as well as of the radial, brachial and temporal arteries were noted. In October, 1922, tortuous pulsating vessels were observed, extending symmetrically from both axillae to the infrascapular and interscapular region. Further examination of the vascular system showed essentially the same findings as at the time of our observations, and therefore the diagnosis of coarctation of the aorta was made.

The patient was admitted to the Beth Israel Hospital on Jan 6, 1930. Although he had dyspnea on slight exertion and a moderately severe cough he had been



Fig 4 (case 2)—*A* showing the dilated arteries of the neck and anterior thorax. *B* showing the superficial vessels of the collateral circulation.

feeling well. He had not worked for eight years. His feet had felt cold constantly for many years, and occasionally, at night, cramplike pains in the calves of the legs had troubled him.

Physical Examination—Examination showed a well developed but under-nourished white man propped up in bed on three pillows, coughing at frequent intervals, and raising a small amount of mucopurulent sputum. There was no respiratory discomfort between paroxysms of coughing. Both pupils were slightly irregular, and the left was larger than the right. Ophthalmoscopic examination revealed advanced tortuosity of the vessels with slight arteriovenous nicking. The lips were slightly cyanotic. The thorax was symmetrical, long and narrow and moderately flattened in the anteroposterior diameter. The infraclavicular and supraclavicular fossae were prominent. Expansion of the lungs was somewhat limited but equal on the two sides. Hoover's sign was positive. The apex

impulse of the heart was felt in the fifth interspace, 10 cm, from the midsternal line. A coarse systolic thrill was felt over the entire precordium. Relative cardiac dulness extended 12 cm to the left and 3.5 cm to the right of the midsternal line. Supracardiac dulness measured 7 cm. On auscultation, a harsh, blowing, systolic murmur was heard over the entire precordium with points of maximum intensity at the apex and in the left second interspace. A murmur of similar quality was heard in the interscapular region. The heart rhythm was completely irregular, the rate was 56 per minute. There was dulness on percussion over both apices of the lungs posteriorly and over the apex of the left lung anteriorly. Numerous persistent fine crepitant râles were heard over the upper part of the back and front of the chest. A few sibilant and sonorous râles were heard over various parts of the chest. All of the superficial arteries were markedly thickened and tortuous. Forcible pulsations were seen over the course of the transverse cervical and subclavian arteries in both sides of the neck and over the subclavian arteries in both infraclavicular fossae (fig 4A). Systolic thrills and murmurs were present over these vessels. The subscapular arteries were dilated and easily palpable. On the right side of the thorax anteriorly, a small pulsating vessel was seen and felt over the costal cartilages of the seventh and eighth ribs (fig 4A). Several pulsating, dilated arteries were seen and felt over both sides of the back, extending posteriorly from the subscapular artery (fig 4B). The pulsation in the larger vessels could be obliterated by pressure on the subscapular artery. The radial pulses were small, equal, synchronous and completely irregular, and there was a deficit in the pulse rate of 4 or 5 beats per minute. On palpation, the pulse waves in the femoral arteries were approximately equal to those in the radial arteries, but the popliteal and dorsalis pedis pulses were barely perceptible. Neither posterior tibial pulse could be felt. Examination of the abdomen gave negative results. The pulsation of the abdominal aorta could not be felt. Rectal examination revealed moderate enlargement of the prostate. Examination of the extremities gave negative results except for a definitely subnormal temperature of the feet. Neurologic examination revealed no abnormalities. The temperature and the respiratory rate were normal during the patient's stay in the hospital. The patient weighed 57.5 Kg, and was 169 cm in height. The vital capacity of the lungs was 1,800 cc.

Clinical Pathology—The red blood cells numbered 4,640,000 per cubic millimeter, and there was 75 per cent of hemoglobin as measured by the Sahli method. The white blood cells numbered 6,900 per cubic millimeter. The differential count of the cells and the number of blood platelets were normal. The blood sugar and nonprotein nitrogen were within normal limits. The Wassermann reaction of the blood was negative. The urine was negative on repeated examinations. The phenolsulphonphthalein excretion was 40 per cent in two hours and ten minutes.

Electrocardiograms—Electrocardiographic tracings showed auricular fibrillation, a ventricular rate of 60 per minute and intraventricular block of the right bundle branch type.

Roentgenograms—Roentgenographic examination of the chest revealed coarse mottling throughout both upper lobes and small cavities in the apex of the right lung. The hilar regions were considerably increased in width and density. There was advanced erosion of the inferior borders of the ribs, extending forward approximately to the posterior axillary line (fig 5). The cardiac measurements as shown by a roentgenogram taken at a distance of 7 feet (213 cm) showed

moderate transverse enlargement of the heart. Fluoroscopic examination of the chest by Dr Samuel A. Robins showed the transverse arch of the aorta somewhat pointed and incompletely visualized.

Pulse Timings—The radial pulse wave appeared approximately 0.05 seconds later than the carotid pulse wave and approximately 0.05 seconds before the femoral pulse wave. Normally, the femoral precedes the radial pulse wave by from 0.01 to 0.02 seconds.

Blood Pressure Measurements—The blood pressure was approximately the same in both arms. The average of a series of measurements was 171 mm. of



Fig. 5 (case 2)—Erosion of the lower borders of the ribs

mercury systolic and 96 mm. of mercury diastolic. On all occasions the systolic pressure measured by the palpatory method was only a few millimeters lower than by the auscultatory method.

The femoral systolic blood pressure was obtained by placing a special cuff, 20 cm. wide, about the middle of the thigh and palpating the dorsalis pedis artery. The average of a series of measurements was 123 mm. of mercury.

The capillary pressure over the sternum was 5 mm., and the arteriolar pressure, 50 mm. of mercury. Over the lateral aspect of the upper part of the arm and upper part of the thigh, the arteriolar pressure was 50 mm. of mercury.

Blood Gas Measurements—Duplicate measurements were made of the oxygen content and capacity of blood from the brachial artery, antecubital vein and femoral vein. The results are presented in table 2.

CLINICAL CONSIDERATIONS

Diagnosis—The diagnosis of coarctation of the aorta was established in both patients by (1) the presence of hypertension in the vessels of the arms as contrasted with the relatively low blood pressure in the legs, (2) the evidence of extensive collateral arterial circulation observed on physical examination and also made apparent by the erosions of the ribs seen in the roentgenograms of the chest, and (3) the diminution and retardation of the arterial pulses in the legs.

Presence of Other Congenital Anomalies—Although the infantile form of coarctation of the aorta frequently is associated with other conspicuous congenital anomalies the adult form is usually free from such gross abnormalities. Careful clinical search for developmental anomalies in our patients was without success, although one cannot state whether any minor abnormalities will be found eventually on post-mortem examination.

Degree of Stenosis—The anatomic degree of stenosis in our patients cannot be stated, but the numerous widely dilated collateral pulsating vessels, the lowered blood pressure in the legs and, in the first patient, the feeble pulsations of the femoral arteries indicated a moderate or extreme degree of coarctation. Abbott⁴ stated that in 155 of the 200 cases analyzed by her, the lumen of the aorta was reduced to 6 mm or less.

Collateral Circulation—In both patients the pulsating vessels over the back, epigastrium and the lower anterior part of the thorax, together with the prominent subclavian and subscapular arteries, indicated that the collateral circulation was accomplished mainly by the following routes: (1) by anastomoses between the superior intercostal artery of the subclavian and the first aortic intercostal that arises from the aorta just below the site of the constriction, (2) by anastomoses between the aortic intercostals and the subscapular artery and its branches, particularly the circumflex scapulae, and (3) by the internal mammary arteries and their anastomoses with the aortic intercostals. The fact that the erosion of the inferior borders of the ribs observed in the roentgenograms of both patients extended only as far forward as the posterior axillary line suggests that the collateral channels between the internal mammary arteries and the aortic intercostals were not extensively developed. In neither patient could the deep epigastric arteries be felt. In the second patient, the prominent transverse cervical arteries indi-

cated that these vessels also played an important rôle in the collateral circulation, probably by way of the anastomoses of the posterior scapular with the subscapular and circumflex scapular arteries

Cardiac Signs—Abbott⁴ found cardiac hypertrophy and dilatation in 150 of the series of 200 cases. It is not an essential feature, however, since patients have lived to the age of 92 with almost complete atresia of the aorta, but without hypertrophy and dilatation of the heart¹¹. In our first patient the heart was of normal size, while in the second it was definitely enlarged. The first patient showed none of the characteristic vascular murmurs usually evident in coarctation of the aorta. The second patient, however, presented the following frequently observed findings: (1) a systolic murmur over the interscapular region similar to the murmur noted by King¹ in his four cases, and (2) a loud, harsh precordial murmur.

Relation between Coarctation of the Aorta and Circulatory Failure—One hundred and forty-eight or 74 per cent of the patients in the cases analyzed by Abbott,⁴ died before or during the fortieth year of life. Our patients did not experience their first symptoms until after the age of 40, and are therefore somewhat unusual in this respect. Throughout the period of growth, and in later years, the collateral circulation evidently had kept pace with the increasing demands. This extraordinary feature was emphasized by Hamilton and Abbott³ and is the more exceptional in our patients in view of the nature of their work. In the first patient the sole manifestation of diminished flow of blood below the coarctation was the appearance of cramps in the legs on unusual exertion several times during the preceding five years. King's¹ first patient likewise had intermittent claudication and, like our patient D. W., did exceptionally heavy work. In our second patient, diminution of blood flow in the lower extremities was indicated by subnormal temperature of the feet and occasional nocturnal cramps in the legs.

In neither patient was the inception of congestive failure associated with any unusual strain. In the first patient, the initial symptoms were those of bronchitis. In the second patient, the relation of auricular fibrillation and pulmonary tuberculosis to the initial appearance of myocardial failure cannot be stated. In both patients the increased work of the heart for many years in the presence of arterial hypertension was probably the primary factor leading to cardiac failure.

Relation Between Arterial Pressure and Degree of Arteriosclerosis—In patients with essential hypertension, arteriosclerosis appears early

11 Reynaud, A. Observation d'une obliteration presque complète de l'aorte, suivie de quelques réflexions, et précédée de l'indication des faits analogues, consignées dans les auteurs, J. hebdomadaire de médecine 1 101, 1828, quoted by Abbott (foot-note 4).

and progresses rapidly. Whether this is due to the increased arterial pressure or to the underlying pathologic process is not clear. It is remarkable that, although arterial hypertension had presumably been present above the level of the coarctation in both of our patients for over forty years, physical examination and roentgen studies failed to disclose any perceptible difference in the degree of arteriosclerosis in the upper and lower parts of the body. In our first patient the radial arteries were thickened but soft and only slightly tortuous. Ophthalmoscopic examination showed only slight arteriosclerosis such as might be expected in a patient of his age without elevated blood pressure. In our second patient, advanced arteriosclerosis was present in all of the superficial peripheral arteries as well as in the retinal vessels.

CIRCULATORY MEASUREMENTS

Retardation and Diminution or Absence of the Femoral Pulse—The retardation and diminution or absence of the femoral pulse are not constant either in their presence or degree. In our patients the time intervals between the apical cardiac impulse and the carotid and radial pulses as measured with the polygraph were within the limits of normal. The rise of femoral pressure, however, occurred 0.15 seconds after the rise of radial pressure in case 1 and 0.05 seconds later than the rise of radial pressure in case 2. Normally, the femoral pulse wave precedes the radial pulse by from 0.01 to 0.02 seconds. Retardation of the femoral pulse was observed also in the patient studied by Railsback and Dock,⁵ who used Frank capsules. In their patient, the femoral arterial pulse followed the radial pulse by 0.02 seconds.

The amplitude of the femoral pulsation is affected not only by the degree of patency of the aorta, but also by the caliber of the collateral pathways and by the directness of the route taken by the blood back to the thoracic aorta. The most extreme cases of coarctation may be difficult to diagnose because the collateral circulation follows a relatively direct route through widely dilated vessels. The facts that the femoral systolic pressure in case 2 approached more closely the brachial arterial pressure and that the pulse wave was less retarded than in case 1 suggest freer communication between the upper and lower parts of the body in the former subject.

Arterial and Arteriolar Pressures—Cardiac energy is transformed into (1) kinetic energy, or energy of flow and (2) potential or pressure energy. Other factors remaining constant, the greater the peripheral resistance, the higher the systolic and diastolic, and therefore the mean arterial, pressure. The elevated arterial pressure in essential hypertension is generally considered compensatory to maintain a normal blood supply.

to the tissues in spite of the increased arteriolar resistance. The arteriolar pressure of both of our patients above the level of the coarctation was 50 mm of mercury by the histamine flare method. This pressure is much lower than that found by Ellis and Weiss⁷ in patients with essential hypertension with similar brachial arterial pressures, but is approximately the same as that observed by them in subjects with normal blood pressure. The results suggest that while increased peripheral resistance may, as in essential hypertension, be responsible for the high blood pressure above the coarctation, this increased resistance is due, not to increased arteriolar resistance, but rather to the resistance offered by the stenosed aorta and the collateral pathways. The normal arteriolar pressure observed in the arms is in accord with this hypothesis rather than with the existence of a reflex mechanism that might be expected to manifest itself by arteriolar constriction and an elevated pressure in the arterioles.

Below the level of the coarctation the arteriolar pressure measured over the lateral aspect of the upper part of the thigh was 45 mm of mercury in case 1 and 50 mm of mercury in case 2. These results are similar to those normally found in the leg. The mean femoral arterial pressure in the first patient was about 80 mm of mercury. The normal arteriolar pressure of 50 mm of mercury indicates a low gradient of pressure in the smaller arteries, the condition approaching that in the precapillary vessels of a normal person in whom the pulsation is markedly diminished, while the volume flow continues normally. The maintenance of normal arteriolar pressure in spite of the low femoral arterial pressure favors a normal gradient of pressure in the arterioles and minute vessels and a more adequate blood supply to the tissues. As will be seen later, the slow velocity of blood flow observed along the larger vessels, and the relatively normal oxygen content of the arterial and venous blood of the leg are in accord with this concept.

Blood Gas Measurements—Normally, the oxygen capacity of arterial blood is about 20 per cent by volume. The blood contains about 19 per cent of oxygen by volume as it leaves the lungs, and is therefore 95 per cent saturated. In passing through the tissues, the blood loses about 5 per cent of oxygen by volume.

In the first patient, the oxygen saturation of the femoral arterial blood was less than the saturation of the brachial arterial blood. This may be due to the utilization of oxygen in the dilated capillary network traversed by the blood in the collateral pathways. The higher oxygen capacity of the femoral arterial blood suggests that slight concentration of the blood occurred in the dilated capillaries of the

collateral circulation. Comparable studies could not be made on the second patient because of lack of cooperation.

The utilization of oxygen in both patients was somewhat greater in the leg than in the arm, but in both subjects the arteriovenous difference in the leg was within the limits of normal¹². This indicates that, in spite of the lowered arterial blood pressure in the leg, there was no significant reduction in the minute volume flow of blood through the capillaries of the lower extremities. A normal femoral arteriovenous oxygen difference could be accompanied by decreased minute volume blood flow only if the metabolic level of the legs of our patients were reduced more than seems possible. The occasional occurrence of intermittent claudication in the first subject and the complaint by the second

TABLE 3—*The Velocity of Blood Flow in the Greater and Lesser Circulation in Case 1*

	Seconds
Pulmonary circulation time including time taken to course through the heart	11
Time from the left ventricle to femoral artery (estimated)	11
Time from the femoral artery to superficial veins of foot	32
Time from the superficial veins of foot to femoral vein	29
Time from femoral vein to right auricle of heart	9
Total circulation time	92

patient of coldness of the feet and nocturnal cramps in the legs indicate, however, that the functional circulatory reserve was limited in both.

Blood Plasma Volume—The volume of blood plasma of our first patient was near the upper limits of normal¹³. A tendency toward an increased volume of plasma is to be expected in the presence of the numerous dilated collateral pathways of the blood.

Velocity of Blood Flow and its Relation to Other Measurements—The following discussion relates mainly to the first patient because measurements of the velocity of blood flow could not be made in case 2 owing to lack of cooperation, and because measurements of the diastolic femoral arterial pressure could not be obtained. It is of considerable interest that the time necessary for the radioactive substance to travel from the heart to the femoral artery was eleven seconds, whereas the time necessary for the material to travel from the femoral vein to the

¹² Harrison, T. R., and Pilcher, C. Studies in Congestive Heart Failure. I. The Effect of Edema on Oxygen Utilization, *J. Clin. Investigation* 8: 259, 1930.

¹³ Thompson (footnote 8) Keith, N. M., Rowntree, L. G., and Geraghty, J. T. A Method for the Determination of Plasma and Blood Volume, *Arch. Int. Med.* 16: 547 (Oct.) 1915.

heart was only nine seconds. Normally, the velocity of blood flow in arteries is approximately twice that in veins¹⁰. The abnormally long time necessary for the radioactive material to reach the femoral artery again indicates the circuitous route traveled by the blood before reaching the lower extremities and the increased resistance it encountered in coursing through the collateral channels.

A period of thirty-two seconds was necessary for the blood to flow from the femoral artery to the superficial vessels of the foot, while twenty-nine seconds were necessary for the radioactive material to flow from a rather large vein on the dorsum of the foot to the femoral vein. This relative slowing of arterial blood flow in the lower extremities is due to the low gradient of pressure in the larger vessels of the legs.

The regulation of blood flow through the minute vessels of the body is at present but imperfectly understood. Normally, the blood pressure in the femoral artery is approximately the same as that in the brachial artery, while the "arteriolar pressure" (the pressure in the larger precapillary vessels) is approximately 50 mm of mercury. The pressure in the veins is approximately zero. Under circumstances requiring augmented blood supply (exercise, etc.), the local increased flow in the legs is probably secured in part by dilatation of the precapillary minute vessels. This results in a higher pressure in at least the first portions of these vessels and an increased gradient of pressure between them and the veins. The difference between the resting arterial and arteriolar blood pressure, according to this hypothesis, is one of the factors in what may be termed the "local circulatory reserve" by means of which increase in local blood supply can be obtained to meet increased demands.

In the legs of patients with coarctation of the aorta, we have found the arteriolar pressure normal but the femoral arterial pressure greatly reduced. The decrease in the arterial-arteriolar difference in pressure indicates that this factor of the normal local circulatory reserve is diminished. Under these circumstances, the arteriolar pressure can be raised only by elevation of the femoral arterial pressure which in turn depends on the aortic pressure above the coarctation and ultimately on the ability of the heart to perform an increased amount of work. If the heart is unable to respond by raising the aortic pressure, the local supply of blood will not be sufficient to meet the increased demands.

It is not altogether surprising, therefore, that the first symptoms of a failing heart may appear in the lower extremities where the circulatory reserve previously has been encroached on. In our patients, as in others observed by King,¹⁴ intermittent claudication, nocturnal cramps

14 King, J. T., Jr. Personal communication.

and diminished temperature of the legs appeared at an appreciable interval before the more usual signs of circulatory insufficiency in the upper parts of the body. Such symptoms may therefore be the earliest indication of a failing heart in patients with coarctation of the aorta, and should call for effective treatment even before the appearance of dyspnea or other evidence of circulatory stasis.

SUMMARY AND CONCLUSIONS

1 Coarctation of the aorta presents an opportunity to compare in the same person the dynamics of the circulation in arterial hypertension above the point of constriction with the dynamics of blood flow under lower pressure below the level of the stenosis. The results of an extensive study of two patients with coarctation of the aorta are presented.

2 The diagnosis was established in both patients by (1) arterial hypertension in the arms as contrasted with the relatively low blood pressure in the legs, (2) evidence of extensive collateral arterial circulation observed on physical examination and also made apparent by the erosions of the ribs seen in the roentgenograms of the chest, and (3) diminution and retardation of the arterial pulses in the legs.

3 Although arterial hypertension presumably had been present above the level of the coarctation in both patients for over forty years, physical examination and roentgenographic studies failed to disclose any perceptible difference in the degree of arteriosclerosis in the upper and lower parts of the body.

4 The arteriolar blood pressure in the arms was normal. This suggests that while increased peripheral resistance may, as in essential hypertension, be responsible for the arterial hypertension above the coarctation, this increased resistance is due, not to increased arteriolar resistance, but rather to the resistance offered by the constricted aorta and the collateral pathways.

5 The velocity of blood flow in the larger arteries of the leg was reduced, and the arterial-arteriolar difference in blood pressure was greatly diminished. According to the measurements of oxygen in the blood, the blood supply to the tissues under resting conditions was nevertheless within the limits of normal.

6 The hypothesis that the small arterial-arteriolar difference in pressure in the legs represents an encroachment on what may be termed the local circulatory reserve is discussed. This condition is contrasted

with that above the level of the coarctation, where a marked difference in arterial-arteriolar pressure prevails

7 Considerations are brought forward that suggest that symptoms of local circulatory insufficiency in the legs such as intermittent claudication and nocturnal cramps may be the earliest indication of a failing heart in patients with coarctation of the aorta, and should call for effective treatment, even before the appearance of dyspnea or any other evidence of circulatory stasis

Since this paper was submitted for publication, both of our patients have died. The diagnosis of coarctation of the aorta was corroborated at necropsy in both, and the postmortem observations will be the subject of a separate communication

Book Reviews

PRACTICAL RADIATION THERAPY By IRA I KAPLAN, B S, M D Price, \$6
Pp 354 Philadelphia W B Saunders Company, 1931

If Kaplan had adhered strictly to his plan of describing only the actual methods of irradiation used by himself in his work at Bellevue Hospital and elsewhere in New York, his manual might be used with considerable confidence. In turning to cancer of the stomach or Gaucher's disease, one might disagree with the author, feeling that it would have been better to list these conditions as unsuitable for irradiation. Nevertheless, one would have to admit that the outlined treatment could probably do no harm, and it might be useful to know that at least one large clinic did attempt to treat patients with these conditions. Unfortunately, however, the author seems to have found it desirable to pad his book with extensive extractions from other texts and journals, and this has involved a good many frank mistakes, to say nothing of questionable judgments.

One expects mistakes in a first printing and is prepared to excuse them. I list below a few of the more obvious ones in this book, which will undoubtedly be corrected before a second printing.

Page 19 "Their (γ -rays') path is not affected by the magnet, nor can they be reflected, refracted, or polarized."

If the clerical assistant who presumably had charge of the padding had enjoyed the most casual acquaintance with modern physical literature, this mistake could have been prevented. It is scarcely necessary to point out that the earliest work on refraction was published in 1896, and that reflection and polarization have long since been commonplace procedures in physical laboratories.

Page 23 "The rays of X-ray and radium may either stimulate, inhibit or destroy living tissues."

While this old dogma is perhaps not thoroughly disproved, it is, to say the least, controversial and should scarcely be reprinted without comment in a book dated 1931.

Pages 23 and 24 "In some cases the cells of a tissue are more affected by a given amount of energy of one range of wavelength than they are by the same amount of energy of another range of wavelength" and "Some respond in different ways, depending upon whether or not the radiation is so administered that a large intensity is coupled with a short period of exposure."

Many people believe that these ideas have been definitely disproved. It hardly seems wise to state only one side of such an important question.

Page 58 In listing the relative merits of valve tube and mechanical rectifier equipment, certain statements are made that were true a year or so ago, but were by no means true in January, 1931, the date of publication. Modern valve tubes will carry as heavy a current as the best mechanical rectifier machine, and automatic discharge devices have done away with the factor of persistent charge in the condensers. The most important advantage of valve tube equipment is not listed, that is, the fact that it is free from high frequency surges so that sphere gap readings really mean something is not mentioned.

Page 63 Modern valve tubes do not require a large amount of resistance in the sphere gap circuit.

Page 130 By far the most serious error that has come to my attention is the description of the Kienbock-Adamson method of treating ringworm of the scalp. The original articles are easily available in any medical library and will be found to stress the idea that treatments should be given to five points on the scalp. Overlapping of the doses used for contiguous areas is an essential part of the plan. Kaplan's abstractor consulted the "United States Army X-Ray Manual" instead of the original literature, and then misread the account in the

manual. As a result, the reader is advised to divide the scalp into four areas for treatment applying the rays to one area at a time and shielding the other three with lead-rubber. It is extremely unlikely that Kaplan actually uses such a method in New York, because owing to the curvature of the skull it would be practically impossible to deliver a full epilating dose to the margin of an area without overexposing the center. It is easy to understand how a careless abstractor would misinterpret the sketches in the "United States Army X-Ray Manual" and would misread "shielding eyebrows, etc."

DIE ENTZUNDLICHE GRUNDLAGE DER TYPISCHEN GESCHWURSBILDUNG IM MAGEN UND DUODENUM By PROF. DR. G. E. KONJETZNY. Price, 18 marks. Pp. 155, with 72 illustrations, some in color. Berlin: Julius Springer, 1930. (Buchausgabe des gleichnamigen Beitrages in "Ergebnisse der inneren Medizin und Kinderheilkunde," volume 37.)

This is a monograph of 155 pages in which are excellently presented the results of the ten year study of ulcer by Konjetzny and his associates, particularly Kalima and Puhl. It begins with a concise review of the older theories of the etiology and pathogenesis of ulcer and then proceeds at once to the investigations carried out in their clinic at Kiel on fresh material obtained at the operating table and submitted to careful histologic study.

The first question asked is whether or not ulcer develops in a previously normal mucosa. It is answered in the negative. Erosions and acute ulcers always accompany chronic ulcers, and they occasionally produce the ulcer syndrome without the presence of a chronic ulcer. These erosions and acute ulcerations are due to an inflammatory process in the mucosa, a gastritis and duodenitis. The erosion develops as the result of polymorphonuclear infiltration just beneath the epithelial membrane. This cellular accumulation increases in size until the membrane is either ruptured or absorbed, an exudate then pours forth and an erosion is formed. Eosinophils and plasma cells slowly appear. The lesion then either heals or becomes more chronic. This process is excellently pictured.

The author then reproduces photographs of lesions, showing all stages of transition from the acute erosion just described to a chronic ulcer, apparently proving conclusively that the process begins in the mucosa and extends into the deeper layers. The entire development is attributed to an inflammatory reaction in which the vascular lesions do not play a rôle and in which peptic activity does not take part. A great deal of space is devoted to arguments on these points. The work is carefully and thoroughly done, the presentation is clear and concise, the illustrations are splendid, and the argument is logical.

In conclusion, Konjetzny discusses the matter of therapy and insists that the best treatment for ulcer is that directed toward the gastritis, rather than toward neutralization of the acid or the control of psychic factors. Surgical intervention should be used only in cases in which complications, such as acute or chronic perforation, hemorrhage and stenosis, have developed. A statement is not made as to the type of surgical intervention recommended, but one infers that subtotal gastrectomy is the procedure of choice. During the ten year period, Konjetzny operated on 28 per cent of the patients with ulcer coming under his care.

This epochal monograph is highly recommended to all students of gastric disease.

STOFFWECHSELKRANKHEITEN By ERICH LESCHÆ, M.D., Professor of Internal Medicine, University of Berlin. Paper. Price, 8 marks. Pp. 130. Dresden: Theodor Steinkopff, 1930.

This little book, which is one of a series prepared especially for the busy practitioner, contains in condensed, but well arranged form, an amazing amount of information. Some of this is more, some less, reliable. It would be impossible for a reader who was untrained in the field of metabolism to disengage theory from fact, speculation from knowledge. The author, particularly in the sections

dealing with therapeutics, adopts a naively uncritical attitude for one who ranks among the leaders in the field of metabolism and endocrinology. Thus, in the section on the treatment for obesity is the serious recommendation of the use by mouth of anterior lobe pituitary substance in pluriglandular combination with ovarian and testicular preparations. The author is one of many who in the reviewer's opinion confuse rather than clarify endocrine problems by resort to pluriglandular, in Leschke's case "plurivegetative," theorizing. It is not to be doubted that all of the glands of internal secretion are affected when one is diseased, but the same can be said of other organs, including the skin, the bones and the muscles. Nor is it to be disputed that functional irregularities of the autonomic nervous system are concerned in many of the disorders of metabolism, but it may be predicted that the primary abnormality in these disorders will be found to be considerably less complex than one would judge from such texts as this one. Certainly conceptions of pluriglandular disturbance have contributed scarcely at all to the advance of factual knowledge of endocrinology and metabolism, while great progress has been made through the separate study of individual processes and individual organs. It is of interest in this connection that epinephrine, thyroxin, insulin and parathormone, to mention only the glandular products of established potency, are developments of the research of a new continent where the authoritative publications in the field of metabolism and endocrinology have been comparatively free from speculation.

TREATMENT OF EPILEPSY By FRITZ TALBOT Price, \$4 Pp 266 New York
The Macmillan Company, 1930

The author has been concerned for some time with the careful and controlled therapy of epileptic patients. In this he has become proficient, because he has understood the modern conception of human metabolism and has applied his knowledge in an attempt to check what is, at least theoretically, a disturbance of metabolism. Dr. Talbot completely reviews the theories as to the etiology of epilepsy, and summarizes in an excellent manner present conceptions. He stresses, naturally, the theories of disturbance in oxygenation, the acidbase equilibrium and the water content. All of these factors may, of course, be part of one underlying disturbance. There does not seem to be enough evidence, however, that in the epileptic patient there is an excessive amount of hydration, a deficiency in oxygen or a tendency to alkalosis. The greatest evidence for these factors as a basis is the therapeutic effect of their reversal. Dr. Talbot considers in great detail the practical application of the ketogenic diet. He leaves nothing of importance unwritten concerning that therapy. Any physician desiring to know the exact technic can find it in this book. The volume is highly recommended to all who are desirous of learning the modern therapy for epilepsy.

HUMAN BIOLOGY AND RACIAL WELFARE Edited by EDMUND V. COWDRY, Professor of Cytology, Washington University, St. Louis Price, \$6 Pp 612
New York Paul B. Hoeber, Inc., 1930

Twenty-seven contributors of recognized authority in their chosen fields have cooperated remarkably well in developing what amounts to a survey course in "human biology" for students, especially medical, and for mature lay readers. The need for such an integration of the many special sciences involved in the complete study of man is charmingly set forth in the keen analysis by Edwin R. Embree, who wrote the introduction. The book proceeds in logical steps from the astronomical consideration of life through the origin and evolution of man, his internal and external adjustments, including such topics as climate, food, urban and rural environment, antisocial behavior, disease, science and industry, and education. The future of man is treated in relation to the inheritance of disease, the biology of populations, the mingling of races, the purposeful improvement of the race and the intentional shaping of human opinion. The vast scope of this book

is evident. Throughout the various chapters runs a true scientific spirit by means of which facts and opinions are kept sharply separated. There is a wealth of information and wisdom to be gleaned, particularly if the reader takes advantage of the selected bibliography. The illustrations are excellent. The style is generally good and the diction always intelligible. It is a pleasant surprise to note how well the scientific contributors have presented their material in a popular style without excessive simplification. This volume hits fairly close to the mark of its purpose.

SBORNÍK PRÁCI NA POČEST SEDESATYCH NAROZENIN Dedicated to PROF LADISLAV SYLLABY. By his pupils and friends. Pp 848. Prague, 1928.

This book, in the spirit of a Festschrift, is dedicated to Prof Ladislav Syllaby, professor of the "Karlova Universita" in Prague, on the occasion of his sixtieth anniversary.

The book contains forty-nine articles written by his pupils and friends in various European countries. At the end of the book there is a bibliography of the writings of Syllaby and his pupils.

The following are some of the important topics taken up in this book: Cyto-morphologic Examination of Blood in Patients with Schizophrenia, by G Altschuller and O Janota, Diagnosis of Active Tuberculosis by Means of Fixation Reaction, by J Jedlicka, Relation Between Lipocytal Coefficient and Osmotic Resistance of Erythrocytes, by V Jedlicka, Comparative Study of Subcutaneous Fat and of Bone-Marrow Fat, by B Kadlec, Medical Treatment of Gastric and Duodenal Ulcer, by H MacLean, Posterior Cervical Lymphatic Syndrome in Cases of Chronic Cervical Arthritis, by J A Barre.

GRENZ RAY THERAPY By GUSTAV BUCKY, M D. Price, \$3.50. New York: The Macmillan Company.

The author describes the physical and physiologic characters of "Grenz" or borderline rays so named because they lie in the spectrum at the lower limit of the roentgen rays. Their wavelength is from 1 to 3 Angstrom units. In penetrability they are so soft that their absorption in air is appreciable. Their therapeutic use is therefore limited to superficial lesions of the skin and to certain systemic diseases in which an erythema acts favorably.

No extravagant claims are made as to the curative effect of the rays. Preliminary reports are made in a considerable list of diseases of the skin in which the results of other radiotherapy are already known. In a goodly number of these, excellent results are claimed. Another list names conditions in which good results were obtained. In a third list bad results are acknowledged.

The Grenz rays are said to present less dangers than the roentgen rays in that cumulative effects are absent and superficial burns heal easily.

HYPERTENSION By LESLIE T GAGER, M D, Clinical Professor of Medicine in the George Washington University, Washington, D C. Price, \$3. Pp 158. Baltimore: Williams & Wilkins Company, 1930.

An excellent and interesting discussion of hypertension is to be found in this monograph. The facts are stated clearly, concisely and accurately. Speculation is reduced to the minimum. The important references are quoted in extenso, so that it is scarcely necessary to go back to the sources. Symptomatology is skilfully delineated with the help of case histories. The chapter on the clinical study of hypertension may well be read over and over again. The author's emphasis on the study of the eyegrounds as the first approach after a careful history and general physical examination indicates his thorough familiarity with hypertension. A complete schema for the clinical study of patients with hypertension is given at the end of this chapter. Prognosis and treatment are discussed along conservative lines. This is an ideal book for medical students of the more intelligent type and for general practitioners who are still curious about disease.

THE CHEST IN CHILDREN By E GORDON STOI OFF, M D Price, \$15
Pp 432 New York Paul B Hoeber, Inc

As an atlas portraying roentgenograms with full descriptions and systematic discussions this book is most creditable, outclassing previous works on this topic in the roentgen literature and equaling the best atlases on other roentgen subjects. While the major number of diseases considered are parallel to conditions also found in the adult and are modified only in their interpretation by the immature anatomy of the child's chest, considerable space is given to conditions most commonly found at an early age as well as those peculiar to childhood. Its illuminating treatment of the whole category of diseases of the chest gives the book instant and lasting appeal not only to the specialist in pediatrics and the roentgenologist but also to the general practitioner who has learned the unusual value of roentgen diagnosis afforded in so many diseases of the chest.

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HYPOGLYCEMIA

THE CLINICAL SYNDROME, ETIOLOGY AND TREATMENT REPORT OF
A CASE DUE TO HYPERINSULINISM *

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The spontaneous appearance of hypoglycemia may result from certain abnormalities of any of the factors controlling carbohydrate metabolism. A survey of the literature indicates that the condition may arise in the most diverse clinical states. In the present article, we undertake a classification of the various types of hypoglycemia, citing illustrative examples of each. Since pancreatic hypoglycemia appears most frequently clinically, this form has been emphasized by a detailed review of the syndrome based on an analysis of the reported cases. A report is given of a patient suffering from hypoglycemia of pancreatic origin. Tables abstracting the details of the available reports on pancreatic hypoglycemia and of leading cases of the other types are included.

In order better to orient the discussion, we present a classification of the diseases in which hypoglycemia appears spontaneously. We wish this to be considered merely as a tentative etiologic framework, for an entirely adequate scheme will be possible only when the mechanisms of the underlying disturbances of carbohydrate metabolism in the various diseases are thoroughly understood.

TYPES OF SPONTANEOUS HYPOGLYCEMIA

Endocrine Hypoglycemia

Pancreatic

A Hyperfunction or hyperinsulinism, diffuse hypertrophy and tumors of the islets, dysinsulinism or dysinsulinosis

B Late diabetes

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C Alimentary hypoglycemia

Suprarenal insufficiency

Pituitary dysfunction

Thyroid insufficiency

Pluriglandular syndromes

Other Types of Hypoglycemia

Hepatic

Muscular dystrophy

Renal diabetes

Lactation and pregnancy

Fatigue

Infections

Terminal hypoglycemia

ENDOCRINE HYPOGLYCEMIA

PANCREATIC HYPOGLYCEMIA A HYPERFUNCTION OF THE ISLETS

Hypoglycemic attacks have appeared spontaneously when the pancreas has shown increased island tissue in two forms, diffuse hypertrophy or circumscribed neoplasia, both malignant and benign, they have also appeared when there was no visible evidence of increased islet tissue. A brief history of the evidence permitting this statement follows.

History of the Concept of Hypoglycemia Due to Hyperfunction of the Islands of Langerhans—Fischler¹ first described hypoglycemic shock under the title "glucoprivative intoxication", this appeared in dogs with Eck fistulas rendered diabetic by phlorizin. Harris,² in 1924, surmised that a clinical condition of hyperfunction of the islands of Langerhans should produce the same symptoms observed after an overdosage of insulin. He reported five cases which he considered of this origin under the terms, "hyperinsulinism" and "dysinsulinism". No pathologic studies were made.

Evidence that diffuse hypertrophy of the islets could cause hypoglycemia was presented by Gray and Feemster³ in 1926. A child born of a diabetic mother died of hypoglycemic shock. The enlargement of the islands in the child's pancreas was considered the result of an attempt to compensate for the hormone missing in the maternal circulation. Diffuse hypertrophy of island tissue occurs also after blockage of the pancreatic duct, de Takats, Hannett, Henderson and

1 Fischler, F. *Physiologie und Pathologie der Leber*, Berlin, Julius Springer, 1916.

2 Harris, S. Hyperinsulinism and Dysinsulinism, *J. A. M. A.* **83** 729 (Sept. 6) 1924.

3 Gray, S. H., and Feemster, L. C. Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child Born of a Diabetic Mother. *Arch. Path.* **1** 348 (March) 1926.

Seitz ⁴ presented evidence that this hypertrophy is accompanied by an increase in the function of the islets. Wilder ⁵ referred to Jaffe's patient who showed hypertrophy of the islands from blockage of the pancreatic duct by a scirrhous carcinoma of the pancreatic head, it is not known whether hypoglycemia developed in this case.

That hypoglycemia could result from a tumor of the islands of Langerhans was demonstrated convincingly in 1927 by Wilder, Allan, Power and Robertson's ⁶ patient. Extracts from the carcinoma and from metastases in the liver yielded insulin. Further proof of the relation of tumors of the islands and hypoglycemia was supplied in 1929 by Howland, Campbell, Maltby and Robinson, ⁷ the removal of a small carcinoma of the islets was followed by cessation of the hypoglycemic attacks. Benign tumors may also produce hypoglycemia, McClenahan and Norris ⁸ described the hypoglycemic death of a Negro whose pancreas contained an adenoma originating in the islands. Not all adenomas of the islands, however, are accompanied by hypoglycemia. Warren ⁹ collected twenty reports of adenomas of the islands of Langerhans in which none of the patients had suffered hypoglycemic shock during life.

Nor may one assume that all cases of pancreatic hypoglycemia are the result of diffuse hypertrophy or tumor of the islets. Hyperfunction of the islands may occur in a pancreas morphologically normal, as was first demonstrated by Finney and Finney ¹⁰. It should be recalled that in the opposite condition of diabetes, changes in the islands are not always demonstrable, so that normal morphology does not prove normal function. It should be emphasized that altered function is of more importance than structural change.

4 de Takats, G., Hannett, F., Henderson, D., and Seitz, I. J. Correlations of Internal and External Pancreatic Secretion, Effect of Isolation of the Tail of the Pancreas on Carbohydrate Metabolism, *Arch Surg* **20** 866 (May) 1930.

5 Wilder, R. M. Recently Discovered Endocrine Diseases, Hyperepinephrinism, Hyperinsulinism and Hyperparathyroidism, *Internat Clin* **1** 293 (March) 1930.

6 Wilder, R. M., Allan, F. M., Power, M. H., and Robertson, H. E. Carcinoma of the Islands of the Pancreas, Hyperinsulinism and Hypoglycemia, *J A M A* **89** 348 (July 30) 1927.

7 Howland, G., Campbell, W. R., Maltby, E. J., and Robinson, W. L. Dysinsulinism, Convulsions and Coma Due to Islet Cell Tumor of the Pancreas, with Operation and Cure, *J A M A* **93** 674 (Aug 31) 1929.

8 McClenahan, W. U., and Norris, G. W. Adenoma of the Islands of Langerhans with Associated Hypoglycemia, *Am J M Sc* **177** 93 (Jan) 1929.

9 Warren, Shields. Adenomas of Islands of Langerhans, *Am J Path* **2** 335 (July) 1926.

10 Finney, J. M. T., and Finney, J. M. T., Jr. Resection of the Pancreas, *Ann Surg* **88** 584 (Sept) 1928.

The terminology of the literature recognizes this distinction. "Hyperinsulinism" implies an increased production of the hormone without stating the cause, "dysinsulinism" suggests a lack of normal control of the release of hormone. It is true that the terms have been used somewhat loosely and no clearcut distinction made. "Dysinsulinism" in the sense just mentioned might exist with a pancreatic tumor, and the term has been so employed by some writers,⁷ or it might exist with a pancreas morphologically normal, as we have seen to be the case. It is precisely for the group of cases showing increased production and abnormal release of insulin in a morphologically normal pancreas that a specific term is needed. One might suggest "insulinosis" or "dysinsulinosis", the actual term is immaterial, provided it is understood to characterize this group alone. If some such term is accepted, it would seem wise to use "hyperinsulinism" in a generic sense for overproduction of insulin, regardless of cause, and "dysinsulinism" generically for abnormal control of insulin production and release, whatever the etiology.

REPORT OF A CASE

The case to be discussed probably belongs to the group for which we have suggested the term "dysinsulinosis". The patient complained of symptoms typical of hypoglycemic shock, studies of her carbohydrate metabolism yielded results similar to those in the reported cases of pancreatic hypoglycemia, and she was completely relieved by the frequent ingestion of foods containing carbohydrate.

Miss A. C., an intelligent and cooperative unmarried woman, aged 39, came to Wauhatchie Sanitarium in July, 1929, complaining of attacks of weakness and unconsciousness with muscular twitching.

The first symptom was a sudden lapse into unconsciousness in 1926. She had omitted supper the night before, when she arose in the morning and tried to walk, she fell, she talked irrationally, her lips trembled, and she was nauseated, then she became unconscious. In one hour she recovered, without treatment, and remembered nothing of the attack. A similar seizure occurred during each of the next three months, during the succeeding two years, she was entirely well.

In May, 1928, the attacks recurred, accompanied by slight convulsive movements of the hands and legs, but never of the jacksonian type. Once or twice diplopia warned of impending symptoms. Recovery was always spontaneous, and no recollection of the event remained. Five or six weekly attacks occurred at this time, in the intervals she was perfectly well.

She then discovered the value of food in aborting and relieving the attacks, in her unconscious states, however, she always resisted efforts to feed her. Rest at home on an augmented diet, but without additional feedings between meals, gave her entire relief.

One month after returning to secretarial work in the fall of 1928, the seizures recurred daily. By that time they had assumed two characteristic forms, a severe and a lighter attack. The lighter episodes consisted of irritability, weakness, perspiration, a tendency to mix words, and drowsiness succeeded by sleep unless food was taken. They appeared before the noon or evening meals. Cookies taken

between meals effectively warded off the attacks. The more severe attacks were the convulsive seizures described.

Various physicians told her that she was a victim of "nerves," information which considerably distressed this woman who had no neurotic tendencies. No change in weight had occurred during the illness, in 1926, she weighed 133 pounds (60.3 Kg), and in 1930, 137 pounds (62.1 Kg).

Then menses were established when she was 12 years of age, they occurred regularly at intervals of three weeks, and were normal in other respects. At the onset of hypoglycemia, they became irregular, being absent as long as three months. Subsequently, although the patient was still ill, they became regular.

No other medical history was elicited, except that she tended to be plump as a child. Measles and mumps were her only previous illnesses. None of the family had any symptoms suggesting hypoglycemia or diabetes. No family history of disease appeared relevant.

Physical examination revealed no abnormality. She was a well developed, somewhat rubicund, middle-aged white woman, who appeared in the best of health. The pupillary reactions were normal, as were the eyegrounds. The thyroid gland was rather prominent, symmetrical and soft, no bruit was heard, no stigmata of hyperthyroidism were present. The breasts were undeveloped. The lungs and heart were normal, except for a faint systolic bruit heard in the second interspace to the left of the sternum. The blood pressure was normal. Nothing abnormal

TABLE 1—*Results of First Sugar Tolerance Test*

Time	Blood Sugar, Mg	Urine Sugar
Fasting	50	0
45 minutes	225	0
60 minutes	230	0
120 minutes	225	0

could be felt in the abdomen. The liver was not enlarged. Neurologic examination for sensation, motor power, reflexes, cranial nerves and mentality gave negative results.

A diagnosis of hypoglycemic attacks was made because of the history of relief on the ingestion of food.

The blood counts were normal. The Wassermann reaction of the blood was negative. The blood sugar level was definitely low, on two occasions the fasting value was 45 and 52 mg, respectively.

The first test for sugar tolerance was made at a time when she was suffering daily hypoglycemic shocks. On July 6, 1929, 175 Gm of dextrose per kilogram of body weight was administered, and the results given in table 1 were obtained on venous blood with the Folin-Wu technic.

The epinephrine test was performed. The blood sugar during fasting was 69 mg. The hypodermic administration of 0.6 cc of epinephrine 1:1,000 was followed by a rise of blood sugar to 99 mg in fifteen minutes and a fall to the fasting level in forty-five minutes. No undue reaction to the test was noted.

Results of the insulin test were. Ten units of insulin, administered while the patient was fasting, caused a drop in blood sugar of from 60 to 45 mg in twenty minutes. There was a slight reaction, consisting of a vacuous, staring expression, slight tremor and perspiration.

Treatment—When the diagnosis was established, the patient was placed on a diet with a high carbohydrate content, and feedings were given between the regular meals and at bedtime. She was immediately relieved, on this regimen there has been no recurrence in a year. She was able to return to work and has apparently been perfectly well.

Since alimentary measures abolished the attacks completely, and since the long duration of her illness seemed evidence against a neoplastic lesion, observation was decided on rather than a partial pancreatectomy. During a year nothing appeared to alter this decision.

A second sugar tolerance curve taken nine months (April 12, 1930) after the first one gave the results shown in table 2.

The difference between the sugar tolerance curve made on admission when she was having a shock daily and that after nine months without symptoms on a diet with a high carbohydrate content is striking. Reference will be made to the possible cause in the discussion of the tolerance curves in the reported cases.

Symptoms of Spontaneous Hypoglycemia of Pancreatic Origin from an Analysis of the Reported Cases—The symptoms of pancreatic hypoglycemia, appearing spontaneously at intervals, resemble those of insulin shock, the intervals tend to become shorter and the seizures more severe. Relief occurs spontaneously or after the ingestion of any food containing carbohydrate, except in severe terminal attacks. Com-

TABLE 2—Results of Second Sugar Tolerance Test

Time	Blood Sugar, Mg	Urine Sugar
Fasting	47	0
45 minutes	145	0
1 hour, 45 minutes	125	0
2 hours, 45 minutes	111	0

monly between the attacks, at least early in the disease, the patient is perfectly well.

The actual seizure may be described as follows. A sense of weakness and extreme fatigue assails the patient, usually after a short fast, if walking, he feels unable to proceed a step farther, a vague nervousness supervenes, the hands tremble, sweat breaks out on the body, an intense hunger proclaims the need for food. Disturbances in vision are frequent: diplopia, dimness and loss of acuity are most common. Vertigo and ataxia may follow, as may nausea, vomiting and epigastric pain. Often an appalling sense of imminent dissolution is experienced. The patient may cry out or sing. Mental confusion becomes apparent to the observer in incoherent speech, irritability and irrational action. Unconsciousness quickly follows, consisting of somnolence or deep stupor, which at times may be momentarily interrupted by questioning or by painful stimuli. The stupor may last for several hours or even for days. More frequently, however, unconsciousness is soon followed by convulsions. The spasms are of the clonic type, beginning in the face with grimacing movements and spreading to all the extremities simultaneously. The convulsions commonly are neither prolonged nor

severe Breathing is said not to be stertorous, and cyanosis is absent, the latter observation probably depends solely on the duration of the convulsion. Foaming at the mouth is frequent, loss of sphincteric control is uncommon. Nystagmus, trismus and inability to swallow have been noted.

The convulsion is usually over in from a few minutes to a half hour, and even without food, the patient, dripping with sweat and saliva, becomes conscious. Recovery is complete, without memory of the accident, however, temporary hemiplegia and occasionally other minor neurologic residua, which clear up after several days, have been noted. Paresthesias of the tongue and lips, following or preceding the attack, have been described.

While in most cases the symptoms develop in the progression described, certain more fulminant attacks resemble completely an epileptic seizure. In other instances the episodes may be mild and innocuous.

Complete abortion of the attack in any stage is produced by the administration of carbohydrate. The only exception is in certain terminal cases. It should be noted that in some persons even the sight of food seems to precipitate symptoms, in our case, during an attack brought on by insulin, the patient seemed distinctly worse for a few moments after eating candy, and then rapidly improved. These observations suggest that there is either an overproduction of insulin in response to a normal stimulus, or an insufficient release of glycogen from storage depots to prevent hypoglycemia.

Recurrence of attacks with increasing frequency is characteristic of pancreatic hypoglycemia. The early seizures are usually separated by considerable time, from two years to several weeks, but over the course of several years or months they become more frequent until the incidence is one or more a day. With the increasing frequency there is a tendency for the attack to become more severe.

Sex and Age Incidence—About twice as many cases have been reported in males as in females. Menstrual irregularity and an increase in the attacks during menstruation have been observed in a few of the women. The most frequent age incidence is from 31 to 50 years. The disease may, however, appear at any age.

Past History—Previous transitory glycosuria, easily controlled by diet and tending to disappear, was present in about a fourth of the patients. One patient¹⁰ was known to have had a high blood sugar content a year before hypoglycemia developed. This observation of a previous glycosuria is the most significant fact gleaned from a study of the past histories. While its relation to subsequent hypoglycemia is not clear, it certainly leads to the hypothesis that the previous elevation of blood sugar eventuated in a hyperfunction of the islets, which

TABLE 3—*Symptoms of the Attack*

Cases	Early			Later		Repeated Attacks	Frequency	Relieved by	Symptoms During Interval
	Nervousness	Weakness Fatigue	Gastro Intestinal Symptoms	Neuro muscular Symptoms	Disturbances of Mental State				
Pancreatic									
1 Harris ² (case 1)	+	+(C O)	Hunger			+	Daily attacks	Food	
2 Harris (case 2)	+	+	Hunger (C O)	Tremor, sweating	Sense of dying	+	Daily attacks	Food	Weakness
3 Harris (case 3)	+(C O)*	+(C O)	Hunger	Tremor		+		Food	
4 Harris (case 4)	+	+(C O)				+		Food	
5 Harris (case 5)	+	+	Hunger			+		Food	
6 Larocle and Bussiere (Rev med chir d mal du foie 1 481 [Nov Dec] 1928)	—	—	Occasional vomiting and dysphagia	Tremor, diplopia, vertigo, trismus	Crying, singing, unconsciousness (once for 3 days)	+	3 months later became progressively more frequent and severe	Food	Weakness, mental impairment
7 Sendraul and Planques (Gaz d hóp 100 1105 [Aug 20] 1927, 1137 [Aug 27] 1927)	—	+(C O)	Nausea, abdominal cramps		Confusion, impairment of speech	+		Food	Asthma
8 Hartmann (M Clin North America 12 1035 [Jan] 1929)	—	+		Diplopia	Semiconsciousness	+	Increasing frequency and severity	Food	Well early gradually grew weaker
9 Zubiran (Medicine, Mexico 9 300 [April] 1929)	+	+	Hunger (C O)	Tremor, vertigo, sweating	Unconsciousness	+	Increased in 1 year from occasional to daily	Food	Well gained weight
10 Finney and Finney ¹⁰	+	+		Tremor, squint, diplopia, vertigo	Crying, singing, confusion, semiconsciousness	+	Initially 68 months, increased in 2½ years to daily	Food	Weakness
11 Allan (case 2) (Arch Int Med 44 65 [July] 1929)	—	+(C O)		Unconsciousness, (C O), stuporous 1 week once	Unconsciousness, (C O), stuporous 1 week once	+	Occasional increased in 3 years to 3 or 4 per week	Food	Weakness

* C O, chief complaint

No.	Author (case)	Sex	Age	Onset	Prodromal	Seizures	Interictal	Postictal	Course	Response to treatment	Remarks
12	Allan (case 3)	—	—	—	—	—	—	—	—	—	Weakness
13	Gammmon and Tenery	+	+	+	Vomiting	Tremor, diplopia, sweating	Crying, stupor	Convulsions, began in face	Before meals	Food	Well
14	Nelson and Eggleston (J A M A 94 860 [March 22] 1930)	—	—	—	—	—	Crying, unconsciousness	"Petit mal" "grand mal"	6 months to daily	Food	Well
15	Nelson and Eggleston (case 2)	—	—	—	—	—	Crying, unconsciousness	"Petit mal" "grand mal"	2 or 3 weeks	Food	Well
16	Nelson and Eggleston (case 3) (also Winans South M J 23 402 [May] 1930)	—	—	—	—	—	Crying, automatism	"Petit mal" "grand mal"	On rising	Food	Well
Tumors of Pancreatic Islands											
17	Wilder, Power, Allan and Robertson ⁶	+	+	+	Hunger (C C)	Tremor, vertigo, diplopia, sweating	Unconsciousness	Convulsions	Fasting	Food, later required dextrose by vein	Weakness
18	Thalhimer and Murphy ¹¹	+	+	+	—	Sweating	Unconsciousness	Convulsions began 1 year after onset	During morning	No evident relation to food	Weakness
19	Howland, Campbell, Maltby and Robinson ⁷	—	+	+	Vomiting	Diplopia, sweating	Unconsciousness	Convulsions, began with facial grimaacing	Fasting	Food	Hemiparesis, recovered
20	McGlenahan and Norris ⁸	—	+	+	Hunger	—	Confusion, difficulty of speech, unconsciousness	Convulsions	Fasting	Food, later dextrose by vein ineffective	Asthenia, loss of memory (C C)
Pituitary											
21	Wilder ¹⁻⁷ (case 1)	—	+	+	Vomiting	Diplopia, tremor, paresis, thesia of face and tongue	Difficulty of speech, hypomania, unconscious 4% to 38 hours	Loss of urinary sphincter control	Before meals	Food	Headaches
22	Wilder (case 2)	—	+	+	Hunger	Tremor, diplopia, vertigo, sweating	Crying, singing, semiconsciousness	Convulsions involving face and arms, loss of urinary sphincter control	On rising	Food	Memory, vision, hearing unimpaired

TABLE 3—Symptoms of the Attack—Continued

Cases	Early			Later		Onset	Repeated Attacks	Frequency	Relieved by	Symptoms During Interval
	Nervousness	Weakness Fatigue	Gastro Intestinal Symptoms	Neuro muscular Symptoms	Disturbances of Mental State					
Pluriglandular										
23 Stenstrom ¹³	—	—			Attack of coma	Rigidity of entire body	—	One attack	Dextrose and epinephrine	
24 Peterson ²⁰	—	+			Unconsciousness	Convulsions	+	Occurred with diarrhea and fever	Food	Headache
25 Longcope ²²	—	—		Vertigo	Excitation, unconsciousness		+	Several a year	Food	Scleroderma
Hepatic										
26 Nadler and Wolfer ³⁷	—	+			Unconsciousness	Convulsions involving face and arms	+	1 to 7 times a day, increasing frequency	Dextrose	Carcinomatous cachexia
27 Griffiths ³⁰ (case 1)	—	—	Vomiting, (O C) dysphagia	Strabismus	Crying, unconsciousness	Convulsions After vomiting	+	1 to 4 times a year	Dextrose	Well
28 Snapper and Van Orsdel ⁴⁰ 29 Wagner and Parnass ⁴¹	No symptoms No symptoms									
Renal										
30 Gibson and Larmer ⁴⁵	+	+		Tremor, sweating		Fasting	+	Very infrequent	Food	Well
Lactation										
31 Stenstrom ⁴⁰	+	+	Hunger	Tremor, sweating	Unconsciousness	Convulsions	+	1 week	Food, weaning child	Well

terminated in hypoglycemic attacks. Occasional glycosuria was noted in three patients at the time of examination. A lowered renal threshold after tests for sugar tolerance was noted once.

A history of gastro-intestinal disturbances appears fairly frequently: flatulence, epigastric burning and constipation. Two patients were operated on for undiscovered peptic ulcers. One had gallstones. Syphilis apparently plays no etiologic rôle. Other reported illnesses appear unrelated etiologically. In two instances a member of the family was similarly affected.

Physical Examination—Physical examinations yielded no significant findings. There is no constant tendency to be over or under weight. The occasional observation of peripheral neuritis, a palpable liver, a hairless chest and sparse pubic hair, a nodular thyroid without other signs, and poor general development appeared to be merely coincidental. In one patient with pancreatic carcinoma and hepatic metastasis, the liver was palpable.

Laboratory Investigation—The degree of lowering of blood sugar bears no quantitative relation to the symptoms. Estimations made during fasting range from 60 mg. to "too low to be read"¹¹. During the attack the average was 43 mg., with extremes of from 95 to 20 mg.

Sugar tolerance curves in seven of nine patients tested reached an abnormal height after the ingestion of dextrose and remained elevated over two hours. The result is comparable to that seen occasionally in normal persons on a low carbohydrate intake. It is possible that repeated insulin shocks deplete the glycogen stores of these patients, thus causing abnormal tolerance curves similar to those obtained after a restricted carbohydrate intake. The slight response of the blood sugar to injections of epinephrine might be regarded as supporting this view. In our case the first test of tolerance showed an abnormal rise and a delayed fall, the second curve made after a high intake of carbohydrate and freedom from shock for nine months was normal. At the later test the glycogen storage may have been more adequate.

To obtain an estimate of glycogen storage, the response of the blood sugar to the injection of epinephrine was observed. No characteristic effect appeared, but in general there was a tendency for the curves to be somewhat low. Such results suggest either diminished glycogen deposits or a faulty mechanism of release. One may not, however, interpret these observations in a strictly quantitative sense.¹² Ephedrine is credited with a slight effect in raising the blood sugar in two cases.

11 Thalhimer, W., and Murphy, F. D. Carcinoma of the Islands of the Pancreas, Hyperinsulinism and Hypoglycemia, *J. A. M. A.* **91** 89 (July 14) 1928.

12 Brill, S. Glycogenolysis Due to Epinephrine in Hepatic Disease, *Arch. Surg.* **18** 1803 (April) 1929.

TABLE 4—Sex, Age, Duration of Symptoms, Past History and Physical Observations

Case	Sex	Age at Onset	Duration of Symptoms	Total Duration After Onset		Glyco suria	Past Medical History	Positive Physical Observations	Weight Above or Below Standard
				Life	Death				
Pancreatic									
1	M	62 yrs	—	—	—	—	Digestive distress, cystitis		—
2	M	72 yrs	—	—	—	+ 1 time	History of syphilis, negative Wassermann reaction of blood previous constipation, bronchitis	Pulse rate 40	—
3	F	39 yrs	—	—	—	+	Gaseousness, healed abscess of lung	Slight exophthalmos, tremor	+
4	F	27 yrs	2 yrs	—	—	0	Chronic appendicitis, tonsillitis		—
5	M	57 yrs	2 yrs	—	—	0	Gallstones pain relieved by food previous meningitis, injured spine in fall, bronchitis		—
6	F	31 yrs	4 yrs	4 yrs	4 yrs	—	Visceroptosis, "coelalgia", attack of polyneuritis	Polyneuritis	+
7	M	57 yrs	5 yrs	5 yrs	—	—	Cramps, nausea		—
8	M	39 yrs	4 yrs	—	7 yrs	0	Wassermann reaction of blood positive, epigastric distress, somnulations	No hair on chest, pubic hair sparse, liver edge palpable	0
9	M	46 yrs	5 yrs	—	—	+ 4 yrs before onset 0 at onset			+
10	F	49 yrs	4 yrs	4 yrs	—	0	Chronic indigestion and constipation, marked nervous instability, two breakdowns, dysmenorrhoea, no pregnancies	Nodular thyroid	+
11	M	49 yrs	3 yrs	3 yrs	—	0			
12	M	43 yrs	4 yrs	4 yrs	—	0			
13	F	36 yrs	3 yrs	3 yrs	—	0	Irregular menses at onset of hypoglycemia		+
14	F	24 yrs	3 yrs	2 yrs	—	0			0
15	M	25 yrs	5 wks	3 mos	—	0			0
16	M	10 yrs	13 yrs	18 mos	—	0			

Tumors of Pancreatic Islands

17	M	38 yrs	18 mos	—	19 mos	+, traces for 3 yrs	Operated for ulcer at 32 yrs, none found, renal stone at 37	Negative, maternal cousin died with similar symptoms	—
18	F	54 yrs	2½ yrs	—	2½ yrs	0	Uterine fibroid	Poorly developed	—
19	F	42 yrs	7 yrs	7 yrs	—	0	Cystitis at 32	Slight loss of weight	—
20	M	41 yrs	6 mos	—	6 mos	0	Loss of memory, died of broncho- pneumonia	—	—
Pituitary									
21	F	42 yrs	3 yrs	3 yrs	—	0	—	Bilateral facial impairment of sen- sation for pain and touch	—
22	F	52 yrs	3 yrs	3 yrs	—	0	Always nervous, hysterectomy at 36	Dermographism, acromeguloid type	—
Pituitary									
23	F	34 yrs	1 yr	1 yr	—	0	Asymptomatic nephritis, no menses	No axillary or pubic hair, hair of the head and eyebrows scanty, posi- tive Babinski sign bilaterally in coma	—
24	F	30 yrs	5 mos	—	5 mos	0	Amnorrhea and loss of axillary and pubic hair after childbirth at 27	No axillary or pubic hair, secondary menstruation, hypertonic muscles, and hands in position of tetany during attack	—
25	M	30 yrs	2 yrs	2 yrs	—	0	—	Scleroderma, bronze skin, hypoten- sion	—
Hepatic									
26	M	30 yrs	1st attack	—	½ mos	0	Primary carcinoma of liver	Large nodular liver, cachexia	0
27	M	2 mos	2 mos	5 yrs	—	0	Convulsions at 1 month	Well developed	—
28	M	?	7 yrs	7 yrs	—	0	—	Undersized, very large liver	—
29	F	?	?	8 yrs	—	1, ultra nated with ketonuria	—	Very large liver, saddle-shaped	—
Renal									
30	F	10 yrs	10 yrs	10 yrs	—	+	—	—	—
Lactation									
31	F	40 yrs	1 yr	1 yr	—	+	Aortic and mitral regurgitation, tuberculosis, glycosuria a few times, nursing a child	Rigidity during coma	—

TABLE 5.—LABORATORY DATA

Case	Blood Sugar, Mg per 100 Cc				Sugar Tolerance Curve	Urinary Sugar	Epinephrine Test	Pituitary Test	Insulin Test	Miscellaneous Observations
	Fasting	During Attack	Lowest	Symptom Level						
Pancreatic										
1	65 70	—	65 70	65 70	High rise, re turned to normal in 3½ hours					
2	65	—	65	—	+ once previously +, none when seen					
3	47 111	95 47	47	—						
4	56	—	56	—	Abnormally high, remained high 3 hours					
5	67	—	67	—						
6	75	66	66	—		6 to 100 in ½ hour	Cured attack	No hyper sensitivity		Fat caused attack, respiratory quotient rose to unity after dextrose, sella turcica normal, basal metabolic rate normal
7	—	62	62	—		No effect in attack	Cured attack			Disks pallid, moderate contraction of temporal fields, basal rate normal
8	—	25 42	12	—	216 at 2 hours					
9	70	58	58	58 (?)	Low rise	Previously +, glycosuria when blood sugar was 117 mg				
10	220 (1925) 184 41 (1926) 30 (1927) 60	20 30	20	—	74, 232, 106 at 2 hours (1926) Normal (1927)	Blood raised to normal	Raised blood sugar	10 units caused attack		Splinal fluid sugar 34 mg, sella turcica normal basal metabolic rate —0 per cent
11	60 40	60 40	40	60		Slight rise in blood sugar, cured attack	Cured attack			Epinephrine cured symp toms
12	50 40	50 40	40	50		Slight transitory rise in blood sugar 69 to 99 in 15 min	Slight transitory rise in blood sugar			
13	45 52	45	45	—	Diabetic type (1926) Normal (1930) Low rise, previous curve reported of diabetic type	+			10 units caused attack	
14	85 101	—	50	—	Low rise, 34 at 2 hours					Basal metabolic rate normal
15	34 90	—	¾	Below 34	Normal					
16	93	—	64	—						
Tumors of Pancreatic Islands	68	55 27	27	55	Remained high at 2 hrs, ¾ at 3 hrs	+, traces for 3 years	No rise in blood sugar	No rise in blood sugar		Fat caused attack in 30 min, respiratory quotient 0.9, went to 1.06 after dextrose, liver weighed 8,300 Gm 8.25% glycogen, metastatic tumor contained insulin, basal metabolic rate +27%, rose to +43% after dextrose

15	"Too low to read"	60	"Too low to read"			Splinal fluid contained 0 cells, Wassermann reaction negative
19	"Too low to read" 60 80	40	—	80 (fasting) to 266, 240 at 3 hrs, postoperatively normal, except 150 at 1 hrs	40 to 110 in 1 hr	Caused rise in blood sugar
20	—	38 42	35	—	—	—
Pituitary						
21	20	20	20	—	No effect on attack	Sella turcica slightly large
22	60	50 90	50	—	Cured attack	Sella turcica slightly large
Pituitary						
23	10 50	15	15	—	Cured attack	Basal metabolic rate —30% (Krogh)
24	40 50	25	20	—	63 to 87 in 1 hr	Plus iron carbon dioxide 97% by volume in attack 66% when improved, 5 cc of blood injected in rabbit did not lower blood sugar, sella turcica normal, basal metabolic rate —20% (Krogh)
25	52	17	17	51	—	Basal metabolic rate —23%
Hypothalamic						
26	25 70	—	25	—	No rise in blood sugar	Van den Bergh normal, bromsulphalein excretion normal, blood cholesterol 176 mg, 50 cc of blood contained no insulin, terminal blood sugar 13 mg, sella turcica normal, basal metabolic rate —9%
27	78 81	25	98	—	No rise in blood sugar	—
28	10 46	—	10	—	Very slight rise in blood sugar caused vomiting	10 units caused shock
29	40	—	40	—	No effect	—
30	65 91	65	68	62	See miscellaneous observations	—
31	40 50	—	10	—	See miscellaneous observations	—
32	—	—	—	—	1, renal diabetes	Double administration of dextrose at 2 hour intervals caused shock in 1 hr
33	—	—	—	—	Lat caused attack	—

TABLE 6—*Outcome of Cases*

Case	Etiology	Treatment	Result
Pancreatic			
1	Hyperinsulinism	Dietary	Cure (1 year)
2	Hyperinsulinism	Food third hour	Cure
3	Hyperinsulinism	Dietary	Cure
4	Hyperinsulinism	Dietary	Cure
5	Hyperinsulinism	Dietary	Cure
6	Hyperinsulinism, no postmortem examination	Dietary	Relief, died in attack without adequate treat- ment, 4 years after onset
7	Hyperinsulinism	Dietary	Cure
8	Hyperinsulinism, no postmortem examination	Food and sugar	Relief, died 7 years after onset
9	Hyperinsulinism	Dietary	Improved
10	Hyperinsulinism pancreas normal	Resection of two thirds of pancreas	Improved
11	Hyperinsulinism pancreas normal	Food nine times per 24 hours, three times at night, resection of two thirds of pancreas	Improved temporarily, returned to preoperative condition
12	Hyperinsulinism, pancreas normal	400-500 Gm. of carbohy- drate per day, resection of two thirds of pancreas (Allan, Bock and Judd J. A. M. A. 9:4 1116 [April 12] 1930)	Unimproved
13	Hyperinsulinism	Dietary	Cure (9 months)
14	Hyperinsulinism	Dietary, suprarenal extract	Cure
15	Hyperinsulinism	Dietary, suprarenal extract	Cure
16	Hyperinsulinism	Dietary, suprarenal extract	Cure
Tumors of Pancreatic Islands			
17	Carcinoma of islands of Langerhans with liver metastasis tumors contained insulin	20-25 Gm. of dextrose per hour by vein required laparotomy	Died, not in hypoglycemia at time
18	Carcinoma of islands of Langerhans, pitu- itary gland normal	Food	Death in coma
19	Carcinoma of islands of Langerhans	Removal of tumor, 300 Gm. of dextrose per day and high diet required preoperatively	Cure (14 weeks)
20	Adenoma of islands of Langerhans round cell infiltration of meninges	Dextrose	Death in coma
Pituitary			
21	Pituitary dysfunction	Food roentgenogram of skull thyroxin, 1 mg. by vein checked attack	Improved
22	Pituitary dysfunction	Food roentgen therapy of skull, pituitary extract	Improved
Pluriglandular			
23	Pluriglandular	Thyroid and supra- renal extracts	Cured, blood sugar normal
24	Pluriglandular, small thyroid and pituitary glands sclerosed supra- renal cortex and ovaries, pancreas normal	Dextrose cured attack	Died, not in shock blood sugar 100 mg
25	Pluriglandular	Thyroid extract	Scleroderma improved, hypoglycemia unimproved
Hepatic			
26	Primary carcinoma of the liver, 70-80% in- volved metastasis to chest, liver deficient in glycogen pancreas normal	Dextrose	Relieved attack, death from carcinoma
27	Hepatic (?), cyclic vomiting	Food and dextrose	Relief at time
28	Hepatic (?)	None	No change
29	Hepatic (?)	None	No change
Renal			
30	Renal diabetes	None	No change
Lactation			
31	Lactation	Weaned child	Cured

No observations of blood sugar after the administration of solution of pituitary appear to have been made, that elevation occurred, however, may be inferred from the fact that, in general, pituitary was effective in relieving shock.

No unusual sensitivity to insulin was noted in the three cases in which it was tested—two showed a slight reaction and one did not.

The sugar content of the spinal fluid was low in two instances during the attacks, 20 and 34 mg, respectively. No estimations of pressure were made on the spinal fluid.

A rise in the respiratory quotient to unity after the administration of dextrose in two of three patients has been adduced as evidence of unimpaired ability to utilize sugar. The basal metabolic rate was normal in four persons and plus 21 per cent in a fifth. The sella turcica was of normal size in five patients in whom roentgenograms were made.

Gastro-intestinal roentgenologic studies and tests of gastric secretion disclosed no striking abnormalities. No observations of peristalsis were made during an attack, in view of the increase of peristalsis after the injection of insulin, and the hunger and epigastric upset experienced by patients during shock, such studies might prove of interest.

Differentiation Between Cases of Hypoglycemia Due to Tumor and Those in Which the Pancreas Seems Morphologically Normal—From an analysis of the case reports no reliable sign or symptom appears on which to base a diagnosis of tumor of the islands as opposed to their hyperfunction in the absence of neoplasia. This may be due in part to the relatively small number of case reports. Howland and his colleagues⁷ were impressed by the erratic behavior in their case of tumor, "as if there were no nervous control" of the production of insulin. In Thalhimer and Murphy's case the attacks showed no relation to food. In the two groups no difference in age incidence was noted. The severity of the seizures was probably somewhat greater in the cases of tumor, though not invariably, asthenia between attacks was also somewhat more marked. The duration of symptoms when the patient was first seen was slightly less for the tumors, averaging 2.5 years with extremes of from 6 months to 7 years as against the average of 4 years for the nontumor group, with extremes of from 1 month to 13 years. Physical examination was of no value in the differentiation except in one patient in whom there was obvious metastasis to the liver. In no instance was the pancreatic tumor palpable. The death rate was of course higher for the tumor group, death occurred, on an average, 15 months after the onset of symptoms with extremes of from 6 months to 2.5 years.

In general, all that may be said is: There is perhaps a tendency for the disease to be more rapid in its development, more severe in

its manifestations, more erratic in behavior and more likely to cause death when tumor is present than in functional hypertrophy of the islands. No differentiation between adenoma and carcinoma seems possible, unless there is evidence of metastasis. There are insufficient reports of hypoglycemia from diffuse hypertrophy of the islands to attempt a differentiation from the other types.

TREATMENT AND RESULTS

The Attack—Relief from the attack is usually easily accomplished by the administration of carbohydrates. In certain severe cases the intravenous injection of large amounts of dextrose is required. Drugs elevating the blood sugar level have proved effective. Epinephrine aborted the seizure in most instances, though it failed in a few, it proved more reliable than any other drug. Solution of pituitary achieves the same result, though less frequently, its action is slower and less marked than that of epinephrine. Ephedrine is still less effective. Suprarenal extract by mouth has recently been recommended. It was previously used with some success in pluriglandular cases,¹³ but as yet the evidence is insufficient to judge its value in hyperinsulinism.

Interval Treatment—Frequent feeding is the mainstay in preventing attacks of hypoglycemia. The diet should be high in carbohydrate. Fat should be used cautiously since it initiated attacks in three patients. In twelve typical cases of hyperinsulinism without proved tumor, in which dietary treatment was given, relief is reported to have occurred in ten, death in two. The intravenous injection of dextrose did not prevent the death of one patient suffering from adenoma. It seems likely that alimentary treatment has no influence on the basic disease process, merely providing enough carbohydrate to prevent shock. If more carbohydrate can be got into the body than the insulin metabolizes, it will be stored and prevent attacks, if more insulin is produced than can be "covered" by carbohydrate in the diet, the treatment will fail.

Roentgen therapy appears not to have been tried except in one case of carcinoma in which it was ineffective.

Surgical Treatment—Partial pancreatectomy was first performed by Finney and Finney¹⁰ in 1928. Allan, Boeck and Judd¹⁴ recently reviewed the subject. Five patients without tumor formation in the pancreas have been so treated. Three of these obtained slight improve-

¹³ Stenstrom, T. Spontaneous Hypoglycemic Coma, *Deutsches Arch f klin Med* **152** 173 (Aug) 1926.

¹⁴ Allan, F. N., Boeck, W. C., and Judd, E. S. Surgical Treatment of Hyperinsulinism, *J. A. M. A.* **94** 1116 (April 12) 1930.

ment but tended to relapse, and two obtained no relief. Resection of a small carcinoma of the islets⁷ is the only instance on record in which operation on the pancreas resulted in complete cure. Two patients with carcinoma of the islets and metastasis to the liver who underwent laparotomy died from one to three months postoperatively. Thus the results of partial pancreatectomy have not, as yet, been satisfactory. In view of this fact, dietary management should first be tried unless neoplasm is suspected. If a dietary regimen fails, one may resort to partial pancreatectomy.

With this review of hyperfunction of the islands we wish to consider two other types of hypoglycemia of pancreatic origin, that of late diabetes and so-called alimentary hypoglycemia.

B HYPOGLYCEMIA OF LATE DIABETES

A terminal hypoglycemia in diabetic patients untreated with insulin and not responding to dextrose has been observed many times. Jonas¹⁵ reviewed several such cases and added one of his own, in which the patient died in hypoglycemic coma ten days after the suspension of insulin therapy. Joslin¹⁶ also dealt with the subject.

C ALIMENTARY HYPOGLYCEMIA

The secondary fall in blood sugar after the ingestion of food has occasionally been sufficiently marked to cause slight symptoms of hypoglycemia. This, however, is exceptional. The degree of fall of the blood sugar after the administration of dextrose has been proposed as a test of islet function.¹⁷

OTHER ENDOCRINE TYPES OF HYPOGLYCEMIA

After this somewhat detailed discussion of pancreatic hypoglycemia, based on a thorough review of the literature, we wish to characterize other types of hypoglycemia. For this purpose a summary of a few leading cases will be utilized, no attempt at an exhaustive review of the literature has been made for the nonpancreatic types. They are not always cleancut in etiology. Their symptoms are those of hypoglycemic shock, but they do not appear in the crescendo of severity and frequency characteristic of the pancreatic type.

Insufficient physiologic knowledge of the relations of various endocrine glands to carbohydrate metabolism makes attempts to evaluate

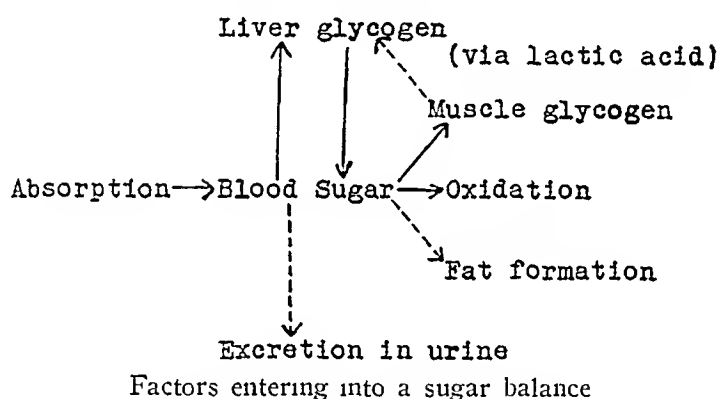
15 Jonas, L. Hypoglycemia, *M Clin North America* 8 949 (Nov) 1924

16 Joslin, E. P. *The Treatment of Diabetes Mellitus*, ed 4, Philadelphia, Lea & Febiger, 1928

17 Depisch, F., and Hasenohrl, R. Beitrag zur Blutzucker-Regulation, *Klin Wchnschr* 5 2011 (Oct 22) 1926

disturbances in these mechanisms clinically somewhat difficult. A carbohydrate cycle has recently been postulated by Cori and Cori¹⁸ (chart). Their hypothesis states "In the muscle the end product of glycogen breakdown is lactic acid, in the liver it is glucose. The most probable point of attack of epinephrin is on the glycogenolytic process." Under its action "blood sugar derived from liver glycogen is utilized in the muscles, while lactic acid derived from muscle glycogen is carried back to the liver to replenish the glycogen that was lost, the end result being an increase in liver glycogen."¹⁹

Somewhat earlier Cannon,²⁰ writing on the sympathetic and suprarenal mechanisms for mobilizing sugar in hypoglycemia, divided the effect of hypoglycemia into two stages. The first stage, in which pallor, a rapid pulse rate, dilatation of the pupils and profuse sweating occurred, was the result of sympathetic stimulation. This sympathetic stimulation had the effect of liberating glycogen from the liver and liberating



epinephrine which, in turn, freed more liver glycogen and raised the level of the blood sugar. The effectiveness of this defense depended on the amount of liver glycogen and the amount of epinephrine present. If the suprarenal content was low, the first defense was weakened. The second stage was the convulsion which liberated more epinephrine and, through liver glycogen, raised the blood sugar level. In view of Cori and Cori's work, one might suppose that the lactic acid formed from muscle glycogen during the convulsion, through resynthesis to glycogen

18 Cori, C. F. The Influence of Insulin and Epinephrine on the Fate of Sugar in the Animal Body, Harvey Lectures, Baltimore, Williams & Wilkins, 1927-1928, series 23, pp. 76-114.

19 A discussion of this work is given in Macleod, J. J. R. Lectures on Physiology of Glycogen and the Role of Insulin and Epinephrine in Carbohydrate Metabolism, *Lancet* 2: 107 (July) 1929.

20 Cannon, W. B., McIver, M. A., and Bliss, S. W. Studies on Conditions of Activity in Endocrine Glands, Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, *Am. J. Physiol.* 69: 46 (June) 1924.

in the liver, could be a further source of blood sugar. Clinically the blood sugar level rises after certain types of convulsion.²¹ These observations, however incomplete, bear on three of the clinical states that we are about to consider: suprarenal insufficiency, hepatic destruction and muscular dystrophy.

SUPRARENAL INSUFFICIENCY

Various writers have attributed the weakness in Addison's disease to lowered blood sugar. Longcope,²² in reviewing the literature, found hypoglycemia frequently present to a marked degree, though by no means universal. The blood sugar tends to remain at a low level without hypoglycemic attacks, though no observations of blood sugar are available, one wonders whether the cases of suprarenal insufficiency with convulsions and epilepsy are due to hypoglycemia. It is possible that the lowered synthesis of epinephrine fails to liberate glycogen from the storage depots.²³

PITUITARY DYSFUNCTION

There remains considerable complexity in the relation of the pituitary body and its diseases to carbohydrate metabolism. Two observations seem authentic. The posterior lobe of the pituitary body is antagonistic to the action of insulin,²⁴ and diminution of posterior lobe secretion either experimentally or clinically results in a high tolerance for sugars.²⁵ Clinically, the syndrome supposed to result from insufficiency of the anterior lobe is accompanied by a high tolerance for carbohydrates.²⁶ Wilder²⁷ recently reviewed the relations of the hypophysis to sugar metabolism. He described a new syndrome, pituitary hypoglycemia, and reported two cases as examples of the condition. Both patients

21 Titus, P., Willetts, E. W., and Lightbody, H. D. Fluctuations in Blood Sugar During Eclampsia. Report of Additional Cases, *Am J Obst & Gynec* **19** 16 (Jan) 1930.

22 Longcope, W. T. Hypoglycemia in Scleroderma, Metabolism in Eight Cases with Reference to Function of Glands of Internal Secretion, *J A M A* **90** 1 (Jan 7) 1928. See also Wadi, W. Ueber Hypoglykämie bei Morbus addisonii, *Klin Wchnschr* **7** 2107 (Oct 28) 1928.

23 Anderson recently described a case of tumor of the suprarenal with fatal hypoglycemia (A Tumor of the Adrenal Gland with Fatal Hypoglycemia, *Am J M Sc* **180** 71 [July] 1930).

24 Burn, J. H. The Modification of the Action of Insulin by Pituitary Extract and Other Substances, *J Physiol* **57** 318, 1923.

25 Cushing, Harvey W. The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott & Company, 1912.

26 Cushing, H. Neurohypophysial Mechanisms from a Clinical Standpoint, *Lancet* **2** 175 (July 26) 1930.

27 Wilder, J. Ein neues hypophysäres Krankheitsbild. Die hypophysäre Spontanhypoglykämie, *Deutsche Ztschr f Nervenhe* **112** 192 (May) 1930.

had slight enlargement of the sella turcica, one displayed slight acromegalic tendencies. The clinical course resembled that of mild hyperinsulinism in the recurring seizures of hypoglycemia. An extract of the anterior lobe of the pituitary was of value in checking attacks.

In Wilder's²⁷ review, several persons with pituitary tumor are mentioned who showed hypoglycemia. Lloyd²⁸ found that a patient with proved pituitary tumor who died in convulsions also had hypertrophy of the islands of Langerhans and the parathyroids. Unfortunately, no estimations of blood sugar were made during the seizures.

THYROID INSUFFICIENCY

The evidence as to the existence and degree of hypoglycemia in hypothyroidism is controversial. Experiments indicate a lowered level for blood sugar following removal of the thyroid, at least in some animals.²⁹ It is also stated that increased tolerance for sugar occurs in myxedema,³⁰ so that large amounts of sugar may be taken without producing glycosuria. Campbell³¹ found definite hypoglycemia and increased tolerance for carbohydrates in two cases of myxedema and in three cases of hypothyroidism following operation for exophthalmos. Administration of thyroid extract raised the fasting sugar level.

On the other hand, in hypothyroidism, cretinism and myxedema, Gray³² observed normal values for sugar during fasting, sugar tolerance curves were high and sustained and were only slightly lower than those of persons with hyperthyroidism. Similar results are reported by Gardiner-Hill, Brett and Smith,³³ in fifteen myxedematous persons, the blood sugar value during fasting was about normal, while sugar tolerance curves were higher and more prolonged than normal. They suggested that the infrequent glycosuria is due to a high renal threshold, an inference that might account for the supposed high carbohydrate

28 Lloyd, P. C. A Case of Hypophyseal Tumor with Associated Tumor-Like Enlargement of the Parathyroids and Islands of Langerhans, *Bull. Johns Hopkins Hosp.* **45** 1 (July) 1929.

29 Bodansky, A., Sutherland, S., and Goldberg, S. A Case of Hyperglycemia in a Thyroidectomized Sheep, *Proc. Soc. Exper. Biol. & Med.* **20** 195, 1922. Werner, G. Variations de la glycémie et de la séro-calcémie dans le syndrome athyroïdien expérimental, *Compt. rend. Soc. de biol.* **100** 926 (April 8) 1929.

30 Sharpey-Schaffer, Sir E. The Endocrine Organs, ed. 2, London, Longmans, Green & Company, pt. 2, p. 35.

31 Campbell, J. W. Low Blood Sugar in Hypothyroid Conditions, *J. Kansas M. Soc.* **30** 365 (Nov.) 1929.

32 Gray, H. Blood Sugar Standards. II. In Conditions Neither Normal nor Diabetic, *Arch. Int. Med.* **31** 259 (Feb.) 1923.

33 Gardiner-Hill, H., Brett, P. C., and Smith, J. F. Carbohydrate Tolerance in Myxoedema, *Quart. J. Med.* **18** 327 (April) 1925.

tolerance of myxedematous persons. In their experience thyroid extract did not raise the level for sugar during fasting, but brought the sugar tolerance curves down toward normal. One may assume, then, that certain myxedematous patients may exhibit hypoglycemia, but the degree is not great and is usually not responsible for symptoms.

PLURIGLANDULAR SYNDROMES

(a) Under the title, "Suprarenal Insufficiency with Dysinsulinism, Gougerot and Peyre³⁴ described six persons with pigmentation, hypotension and feebleness before meals associated with mild hypoglycemia (from 67 to 56 mg) and relieved by sugar. Syphilis was considered to play an important causative rôle. No fatalities occurred. No pathologic data were given.

(b) Longcope²² reported hypoglycemic attacks in a man with scleroderma who had a bronzed skin, hypotension and a low basal metabolic rate. He drew attention to the similarity to Addison's disease. Thyroid extract improved the scleroderma and elevated the metabolism, but had no effect on the blood sugar or the attacks.

(c) Stenstrom¹³ described a young woman, amenorrheic, without axillary or pubic hair and with scant eyebrows, who suffered a single attack of hypoglycemic coma. The basal metabolic rate was low. She was brought out of a rigid coma by the injection of epinephrine, and was kept free from attacks, with normal blood sugar, by the administration of suprarenal and thyroid extracts.

(d) In a somewhat similar case of Petterson's,³⁵ a young woman, amenorrheic and with scant hair, lapsed into hypoglycemic coma. She was revived and had no further seizures, but died three months later with a normal blood sugar. Small pituitary and thyroid glands, with an altered suprarenal cortex and sclerosed ovaries, were found at autopsy. Injection of her blood into a rabbit caused no fall in blood sugar.

OTHER TYPES OF HYPOGLYCEMIA

HEPATIC HYPOGLYCEMIA

In addition to the foregoing discussion of the rôle of the liver in maintaining blood sugar, reference may be made to the excellent work of Mann³⁶ and his colleagues in clarifying this relation. Hence one

³⁴ Gougerot, H. and Peyre, E. Suprarenal Insufficiency with Dysinsulinism. New Pluriglandular Syndrome, *Compt rend Soc de biol* **93** 1202 (Nov 20) 1925.

³⁵ Petterson, A. S. Ein Fall von spontanem hypoglykämischen Koma, *Acta med Scandinav* **69** 232, 1928.

³⁶ Mann, F. C. The Effects of Complete and of Partial Removal of the Liver, *Medicine* **6** 419 (Dec) 1927.

might expect hypoglycemia from destructive lesions of this great glycogen depot. This occurred in a case recently reported by Nadler and Wolfer³⁷. A patient whose liver was riddled with carcinoma suffered attacks of extreme hypoglycemia during the last three months of life.

Josephs³⁸ had previously reviewed the literature of recurrent vomiting in children, finding various degrees of associated hypoglycemia. He was inclined to view the fatty degeneration of the liver found in fatal cases as a possible cause of the hypoglycemic seizures. Certain cases of hypoglycemia in children reported by Griffith³⁹ and that of Snapper and van Creveld⁴⁰ may belong in this group.

Wagner and Parnass,⁴¹ in the first report of clinical hypoglycemia that we have found in the literature, described a child whose only symptoms were weakness and a large abdomen due to a tremendous liver. Glycosuria and hyperglycemia after meals alternated with extreme hypoglycemia and ketonuria on fasting. Although the blood sugar was "absent" at times, no symptoms of shock were noted.

Though we shall not review the hypoglycemic effects of hepatotoxic substances, the observations of Le Count and Singer⁴² on alcoholic addicts are pertinent. The fatty infiltration uniformly found in the liver and the death in convulsions of one patient with a blood sugar content of 67 mg suggested that sudden death in alcoholic persons and "whiskey fits" might be due to hypoglycemia. They considered that the glycogen-storing capacity might be reduced by the fatty infiltration caused by alcohol. This hypothesis must await further study.⁴³

MUSCULAR DYSTROPHY

In view of Cori and Cori's hypothesis of muscle glycogen as a source of blood sugar, referred to, one might seek for hypoglycemia in destructive muscular lesions. Scheimann⁴⁴ investigated the carbo-

37 Nadler, W. H., and Wolfer, J. A. Hepatogenic Hypoglycemia Associated with Primary Liver Cell Carcinoma, *Arch Int Med* **44** 700 (Nov.) 1929.

38 Josephs, H. Spontaneous Hypoglycemia in Childhood, *Am J Dis Child* **38** 746 (Oct.) 1929.

39 Griffith, J. P. C. Hypoglycemia and the Convulsions of Early Life, *J A M A* **93** 1526 (Nov. 16) 1929.

40 Snapper, L., and van Creveld, S. Un cas d'hypoglycémie avec acétonémie chez un enfant, *Bull et mem Soc med d hôp de Paris* **52** 1315 (July 26) 1928.

41 Wagner, R., and Parnass, J. K. Ueber eine eigenartige Störung des Kohlen-Draststoffwechsels, *Ztschr f d ges exper Med* **25** 361, 1921.

42 Le Count, E. R., and Singer, H. A. Fat Replacement of the Glycogen in Liver as a Cause of Death, *Arch Path* **1** 84 (Jan.) 1926.

43 Cammidge, P. J. Hypoglycaemia, *Lancet* **2** 1277 (Dec. 20) 1924.

44 Scheimann, M. S. Der Kohlenhydratumsatz bei der Dystrophia musculorum progressiva, *Arch f Psychiat* **87** 665, 1929.

hydrate metabolism in eight persons with progressive muscular atrophy and found two with hypoglycemic levels. No symptoms or shock appeared.

RENAL DIABETES

Many authors have found a tendency toward low blood sugar in renal diabetes.⁴⁵ Usually the degree of depression is slight and no symptoms are associated. The sugar lost in the urine apparently is not responsible, for excretion of large amounts of sugar is not always associated with shock.⁴⁶ Mild symptoms from the hypoglycemia occurred in Gibson and Larimer's⁴⁷ patient. Certain of the fifty cases of mild hypoglycemia studied by Hoxie and Lisherness⁴⁸ probably were due to renal glycosuria.

LACTATION AND PREGNANCY

Hypoglycemic seizures in a nursing mother who also had pulmonary tuberculosis and valvular heart disease were delineated by Stenstrom.⁴⁹ The attacks were lessened by cutting down the high amount of fat in the diet, and eliminated by weaning the child. After weaning, the same diet no longer produced the seizures.

Relative hypoglycemia associated with eclampsia was observed by Titus, Willetts and Lightbody.²¹ Sharp drops in the blood sugar preceding convulsions were noted, but the level of hypoglycemia was not low. A rise of blood sugar followed the convulsion. It seems unlikely that the convulsion results from the hypoglycemia.

FATIGUE

Physical exhaustion in marathon runners is attributed to the production of hypoglycemia by Levine, Gordon and Derick.⁵⁰ Less conspicuous are the cases of hypoglycemia from chronic fatigue, but many of Hoxie and Lisherness'⁴⁸ cases could be explained on no other basis.

45 Jonas, L. Renal Glycosuria, *M. Clin. North America* **6** 1079 (Jan.) 1923.
Gibson, R. B., and Larimer, R. N. Hypoglycemic Symptoms Provoked by Repeated Glucose Ingestion in a Case of Renal Diabetes, *J. A. M. A.* **82** 468 (Feb. 9) 1924.

46 Jonas (footnote 45, first reference)

47 Gibson and Larimer (footnote 45, second reference)

48 Hoxie, G. H., and Lisherness, G. M. Hypoglycemia, *Am. J. M. Sc.* **173** 220 (Feb.) 1927.

49 Stenstrom, T. Spontane hypoglykamische Reaktion bei stillender Frau. *Deutsches Arch. f. klin. Med.* **153** 181, 1926.

50 Levine, S. A., Gordon, B., and Derick, C. L. Some Changes in the Chemical Constituents of the Blood Following a Marathon Race, *J. A. M. A.* **82** 1778 (May 31) 1924.

INFECTIONS

Certain infections, such as diphtheria, cholera, typhoid, late tuberculosis and experimental trypanosomiasis, are accredited by some writers with producing hypoglycemia. It is not within our scope in this paper to investigate extraneous causes of hypoglycemia.

TERMINAL HYPOGLYCEMIA

Terminal hypoglycemia in diabetes has already been mentioned. Ashe, Mosenthal and Ginsberg⁵¹ discussed a case in which the patient died in uremia with a blood sugar level of 30 mg.

SUMMARY

Hypoglycemia may result from several types of abnormal mechanisms: (1) from disturbance of carbohydrate control (*a*) through overproduction of insulin by hyperfunction, hypertrophy or tumor of the islets or (*b*) through loss of the substances that are antagonistic to insulin as in hypo-adrenalinism, hypothyroidism, pituitary dysfunction or combinations of these, (2) from interference with storage or release of glycogen in the depots of the body—the liver and muscles—or from depletion of glycogen from physical effort, (3) from conditions in which dextrose is lost from the body as such, e. g., in renal diabetes, or as other sugar, e. g., in lactation. The most important cause, by far, is that of overproduction of insulin.

In attempting to distinguish the various types of hypoglycemia, one must look for concomitant evidence of disorders of the endocrine glands or glycogen depots or of the loss of carbohydrate. Hypoglycemia of pancreatic origin presents a typical syndrome recognized without difficulty.

The point of distinction between hypoglycemic seizures and other convulsive states rests on the depressed blood sugar level. A history of relief from the ingestion of food often suggests this investigation.

A review of the clinical manifestations of pancreatic hypoglycemia has been attempted, based on the cases reported in the literature. A typical case of hyperinsulinism has been added to this group. In order to contrast pancreatic with other forms of hypoglycemia, examples of the various types of spontaneously appearing hypoglycemia have been cited. Outlines of the details of the available reports of pancreatic hypoglycemia and of leading cases of the other types are given in the accompanying tables.

⁵¹ Ashe, B. I., Mosenthal, H. O., and Ginsberg, G. Hypoglycemia, With and Without Insulin, With and Without Symptoms, *J. Lab. & Clin. Med.* **13**: 109 (Nov.) 1927.

THE EFFECT OF HIGH ALTITUDES ON THE CHOLESTEROL, LECITHIN AND FATTY ACIDS IN THE PLASMA OF HEALTHY MEN^{*}

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AND

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In many clinical conditions involving the hematopoietic organs, cholesterol and lecithin show deviation from the normal, indicating that in some way, directly or indirectly, the metabolism of these substances may be intimately related to the functioning of the blood-forming tissues¹. A very small amount of data is available, however, which definitely correlate a functional physiologic state of the hematopoietic organs with the lipoids of the blood.

It is well known that exposure to low barometric pressure, that is, to low oxygen tension, will cause a stimulation of the blood-forming organs. This has been repeatedly verified² since Viault³ demonstrated that the peripheral blood of man in passing from a low to a high altitude shows an increase of red blood cells and hemoglobin. Zuntz and his associates⁴ and Dallwig, Kolls and Loevenhart⁵ also found evidences of stimulation of the bone marrow in animals subjected to low oxygen tension. From their experiments they concluded that "the bone marrow has no power to adapt itself to decreased oxygen supply since the increased rate of erythrocytes and haemoglobin formation continue indefinitely for a given oxygen tension". This has been substantiated from a different angle by the results of Barcroft and the other members of the Cerro de Pasco Expedition⁶ who demonstrated that at an alti-

^{*} Submitted for publication, Oct 30, 1930

^{*} From the Thorndike Memorial Laboratory of the Boston City Hospital, and the Leadville Expedition from the Harvard Fatigue Laboratory, D B Dill, Director

^{*} Anna Ryan, A B, gave us technical assistance

1 Muller, G L. *Medicine* **9** 119, 1930

2 Schneider, E C. *Physiol Rev* **1** 631, 1921

3 Viault, F. *Compt rend Acad d sc* **111** 917, 1890, **114** 1562, 1892

4 Zuntz, N, Loewy, A, Muller, F, and Caspari, W. *Hohenklma und Bergwanderungen*, Berlin, Bong & Company, 1906

5 Dallwig, H C, Kolls, A C, and Loevenhart, A S. *Am J Physiol* **39** 77, 1915-1916

6 Barcroft, J. *The Respiratory Function of the Blood. I. Lessons from High Altitudes*, London. Cambridge University Press, 1925

tude of 14,200 feet, concomitant with the increase of red cells and hemoglobin in the blood, there was an increase of reticulocytes to about 49 per cent in normal persons. However, an increase of the absolute number of reticulocytes was also found constantly in the permanent residents of the region, and it was concluded that the rate of production of red blood cells from a given quantity of bone marrow was the same, but that in high altitudes the active bone marrow was increased in volume. Barcroft and his associates thought, therefore, that the reticulocytes are probably not extruded in greater numbers than correspond to the increase of the number of erythrocytes in the peripheral blood.

All the evidence thus points to an active stimulation of the blood-forming organs or to an extension of the normally functioning bone marrow when man or animals are subjected to low oxygen tension.

EXPERIMENTAL WORK

This paper deals with the amount of cholesterol, lecithin and fatty acids in the blood of four healthy young men during an expedition to Mount Elbert, Colorado in the summer of 1929. The ascent to the 10,000 foot level was made by automobile or train, and from the 10,000 foot level to the 14,000 foot level by horse most of the way. The lipoids have been correlated with the oxygen capacities of the blood as a measure of the functioning hemoglobin, and occasionally with the red blood cell count. Material for the determinations was collected by members of the expedition at a 10,000 foot level, and in two of the subjects, for a short time, at a 14,000 foot level. Specimens of the blood were taken twelve hours after arrival on the mountain at the 10,000 foot level but, unfortunately, control determinations at sea level were not obtained before the ascent. Determinations of the lipoids on three of the subjects at sea level were made one year later in the early summer of 1930 so as to exclude any possible seasonal effect.⁷ The cholesterol was determined by the method of Bloor, Pelkan and Allen,⁸ the lipid phosphorus by the method of Whitehorn⁹ and the oxygen capacity by the method of Van Slyke¹⁰. The results obtained are set forth in the tables with explanatory data.

The examination of these tables revealed that with the methods used no demonstrable change occurred in the amount of cholesterol during the stay at the 10,000 or the 14,000 foot level. One subject seemed to show a slight fall of the lecithin phosphorus during the first week of

⁷ Currie, A. N. *Brit J Exper Path* **5** 293, 1924.

⁸ Bloor, W. R., Pelkan, K. F., and Allen, D. M. *J Biol Chem* **52** 191, 1922.

⁹ Whitehorn, J. C. *J Biol Chem* **62** 133, 1924.

¹⁰ Van Slyke, D. D., and Stadie, W. C. *J Biol Chem* **49** 1, 1921.

TABLE 1—*Lipoids and Oxygen Capacity of Blood in A F*

Days	Cholesterol, Mg per 100 Ce Plasma	Leecithin Phos- phorus, Mg per 100 Ce Plasma	Fatty Acids, Mg per 100 Ce Plasma	Oxygen Capacity, per Cent by Volume	Red Blood Cells per C Mm	Time of Obtaining Blood Sample	Comment
1	170	8.8	377	20.10	5,670,000	9 00 a m	10,000 feet above sea level, first blood sample taken 12 hours after arrival
2	170	8.3	377	20.80	4,680,000	9 00 a m	
3	152	9.2	480	20.96	5,880,000	9 00 a m	
4	163	9.8	374	20.60	4,970,000	9 00 a m	
5	159	10.0	441	20.88	5,190,000	9 00 a m	
6	166	8.9	416	20.93	5,140,000	9 00 a m	
8	182	9.1	445	20.45	5,720,000	9 00 a m	
11	169	10.8	415	21.85		9 00 a m	
21	167	10.1	389	20.77		10 00 a m	
24	178	9.9	422	21.33		2 30 p m	
0	170	9.4	442	19.80		3 30 p m	14,000 feet above sea level
1	163	8.7	441	19.80		3 00 p m	First blood sam- ple taken 1 hour after arrival sub- ject rode horse back to the top
2	157	9.1	422	19.25		1 00 p m	
13				19.65			10,000 feet above sea level

TABLE 2—*Lipoids and Oxygen Capacity of Blood in A M P*

Days	Cholesterol, Mg per 100 Ce Plasma	Leecithin Phos- phorus, Mg per 100 Ce Plasma	Fatty Acids, Mg per 100 Ce Plasma	Oxygen Capacity, per Cent by Volume	Red Blood Cells, per C Mm	Time or Obtaining Blood Sample	Comment
1	153	7.5	361	21.67	4,760,000	9 00 a m	10,000 feet above sea level, first blood sample taken 12 hours after arrival
2	142	7.5	425	21.72	4,970,000	9 00 a m	
4	133	7.4	418	20.49	4,950,000	9 00 a m	
5	152	7.1	434	20.54		9 00 a m	
6	169	7.3	460	20.78		9 00 a m	
7	150	7.9	403	21.83		9 00 a m	
8	149	8.8	422	21.97		9 00 a m	
13	173	7.8	441	21.25		9 00 a m	Arterial blood
16	144	7.8	476	20.98		10 00 a m	
19				20.33			
20	156	8.3	508	19.87		2 30 p m	
0	152	10.3	483	20.60		3 30 p m	14,000 feet above sea level
1	135	9.4	476	20.49		3 00 p m	First blood sam- ple taken 1 hour after arrival
2	139	8.3	467	20.25		1 00 p m	Subject rode horseback to top
4	153	9.0	469	20.66		7 00 a m	
16				22.10			10,000 feet above sea level
1	127	9.3	424			9 00 a m	Sea level
3		10.8	405			9 00 a m	
8	123	9.2	408			9 00 a m	
10	126	9.1	437			9 00 a m	

his residence at the 10,000 foot level (table 3), while a slightly higher level of lecithin phosphorus was observed at the 14,000 foot level in another (table 2) than at the 10,000 foot level. These variations, however, are slight and not uniform. Neither can any significant change be demonstrated in the oxygen capacity of the blood that can be ascribed to the change of the oxygen tension of the air.

TABLE 3—*Lipoids and Oxygen Capacity of Blood in J H T*

Days	Cholesterol, Mg per 100 Cc Plasma	Lecithin Phosphorus, Mg per 100 Cc Plasma	Fatty Acids, Mg per 100 Cc Plasma	Oxygen Capacity, per Cent by Volume	Red Blood Cells, per Cc Mm	Time of Obtaining Blood Sample	Comment
1	166	8.6	377	22.45	5,680,000	9 00 a m	10,000 feet above sea level first blood sample taken 12 hours after arrival
2	159	9.1	361	22.55	5,460,000	9 00 a m	
3	173	8.2	298	23.23	5,780,000	9 00 a m	
4	163	8.4	322	23.55	5,860,000	9 00 a m	
5	170	7.9	373	22.88	5,710,000	9 00 a m	
6	178	7.7	405	23.76	5,600,000	9 00 a m	
8	169	7.0	338	23.27	5,340,000	9 00 a m	
9	153	7.5	344	21.85		9 00 a m	
11				23.26		9 00 a m	
13	150	8.3	368	24.18		9 00 a m	
17	142	8.3	357	21.74		9 00 a m	
39				22.69			
1	195	8.7	454			9 00 a m	Sea level
2	188	8.4	434			9 00 a m	
3	184	8.0	405			9 00 a m	
4	197	8.7	405			9 00 a m	

TABLE 4—*Lipoids and Oxygen Capacity of Blood in D B D*

Days	Cholesterol, Mg per 100 Cc Plasma	Lecithin Phosphorus, Mg per 100 Cc Plasma	Fatty Acids, Mg per 100 Cc Plasma	Oxygen Capacity, per Cent by Volume	Time of Obtaining Blood Sample	Comments
1	133	7.9	425	19.65	9 00 a m	10,000 feet above sea level First blood sample taken 12 hours after arrival
2	132	8.1	438	20.00	9 00 a m	
3	135	8.2	426	19.71	9 00 a m	
4	134	7.7	416	19.87	9 00 a m	
21				20.68	9 00 a m	
1	145	7.9	395		9 00 a m	Sea level
3	141	8.1	395		9 00 a m	
8	143	7.9	408		9 00 a m	
11	144	7.7	438		9 00 a m	

In the three subjects in whom the lipoids of the blood were determined at the sea level, the average cholesterol values, when compared with those obtained on Mount Elbert, were slightly higher in two and lower in one. These results thus are contradictory, and whether any significance can be attached to them is problematic. It is, however,

noteworthy that the amounts of cholesterol in healthy men vary considerably from each other, but that they are regulated at a particular level during a given period in the same person in a fairly constant manner.

The lecithin phosphorus in two subjects was practically the same at sea level and at the 10,000 foot level. In a third subject (table 3) the average lecithin phosphorus was 7.7 mg per hundred cubic centimeters of plasma at the 10,000 foot level and 9.2 mg at the 14,000 foot level, as contrasted with 9.6 mg per hundred cubic centimeters at sea level. No trend that seemed of any significance could be made out in the level of the fatty acids.

COMMENT

A very small amount of data is available on the lipoids of the blood in high altitudes. Rabbeno,¹¹ making determinations on himself, came to the conclusion that on Col d'Olen (altitude 10,000 feet) the cholesterol remained unchanged for from three to four days, and then increased. This phenomenon was more marked in November than in the summer months, so that the lower temperature must be considered as well as the rarefaction of the air. Schemensky,¹² studying his own blood at sea level and at Davos (altitude about 5,100 feet), thought that there was a slightly higher cholesterol level at Davos. From the examination of his figures, however, there does not seem to be any clearly established change. His examinations include two other persons with one determination each at Berlin and at Davos which showed respectively 135 and 165 mg per hundred cubic centimeters of plasma at Berlin and 178 and 246 mg per hundred cubic centimeters of plasma at Davos. Four residents at Davos gave values between 235 and 481 mg of cholesterol per hundred cubic centimeters of plasma (one determination each) while two tuberculous patients had 195 and 246 mg per hundred cubic centimeters of blood. Schemensky concluded that in high altitudes there are greatly increased values of cholesterol, almost equal to those seen in nephritis. Decreased atmospheric pressure alone caused no change in cholesterol in animals, but one dog exposed to sunlight had a marked increase of cholesterol in the blood. Schemensky therefore suggested that light may play some part. Guinea-pigs at sea level had from 30 to 40 mg of cholesterol per hundred cubic centimeters, while guinea-pigs at Davos showed from 71 to 88 mg per hundred cubic centimeters of blood. As the altitude of Davos is only about 5,000 feet, distinct physiologic changes due to decreased oxygen tension are not

11 Rabbeno A. Arch d'sc biol 9 161, 1926, abstr, Ber u d ges Physiol 40 409, 1927.

12 Schemensky, W. Ztschr f klin Med 111 205, 1929.

to be expected. On the other hand, Sundstroem and Bloor¹³ reported a decrease of the lipid phosphorus of approximately 13.2 per cent in animals subjected to low barometric pressure. They suggested that the first phase of stimulation of the bone marrow resulting from a lowering of the oxygen tension is an enrichment of the erythropoietic organs with lipid material.

From our data it may be concluded that, with the methods used, no consistent significant change can be demonstrated in the amount of lipoids in the blood of healthy men subjected to low barometric pressure at altitudes of 10,000 and 14,000 feet. This may be due to the fact that an altitude of 10,000 feet is too low to produce any marked physiologic changes, as suggested by Barcroft,⁶ and that the residence of our subjects at the 14,000 foot level was of too short duration. As no marked stimulation of the hematopoietic organs was observed, as evidenced by the unchanged level of red blood cells and hemoglobin (reticulocyte counts were not made), the results obtained do not throw any light on the relation between increased blood formation under physiologic conditions and the lipoids of the blood.

CONCLUSIONS *

Cholesterol, lecithin phosphorus, fatty acids and the oxygen capacity of the blood were determined in four healthy men at sea level and during several days' residence in Leadville, Colorado, 10,000 feet above sea level, and later in two subjects at Mount Elbert at a 14,000 foot level. No consistent significant changes were observed in these constituents of the blood that could be ascribed to the high altitude.

13 Sundstroem, E. S., and Bloor, W. R. *J. Biol. Chem.* **45** 153, 1920.

A BIOMETRICAL ANALYSIS OF TWO THOUSAND FIVE HUNDRED AND SIXTY-TWO COMPLETE EXAMINATIONS OF THE BLOOD *

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Estimations of the hemoglobin and morphologic constituents of the blood have been determined on large groups of normal persons under varying conditions. Further statistical inquiry would be useless, yet there are certain data, acquired in semipathologic investigations, that are still open to fruitful inquiry. It is with events of this sort that the present paper concerns itself.

There is a large group of ambulant persons, neither ill nor well, who every day subject themselves to medical inquiry. Among them major physical damage is the exception, and subjective functional disturbance the rule. They are the people with elusive focal infection, malnutrition, disturbed gastro-enterologic function, neurocirculatory asthenia, etc. Persons of this type as well as others with organic lesions in whom no marked changes in the blood were evident form the basis for the present survey. No frank diseases of the blood or other unusual variants were included in the 2,562 cases here recorded. Marked leukocytosis or leukopenia, over 15,000 or below 4,000, was ruled out. Sharp anemias or polycythemic conditions were likewise not included.

The object in the present study was to measure the frequency distribution in the variation of the separate elements concerned in an examination of the blood by determining the constants which would give a sufficient picture of the central or typical condition with respect to each element. The three constants ascertained for each element were, in turn, the arithmetical mean, the median and the mode. By definition the mean supplies the center of gravity of the frequency distribution, the median is the value above and below which exactly 50 per cent of the variates fall, while the mode establishes a figure exhibiting the maximum frequency of occurrence. The degree of scatter of the observed variates was determined by the computation of the standard deviation as well as the general coefficient of variation in each case. The significance of the established constants was checked by the estimation of the probability of error in the case of both the mean and the median for all observed elements. It was hoped that in this way true values could be

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* From the Miller Hospital Clinic

established and the comparative accuracy of the arithmetical mean for observations of this type be determined. The first effort, then, was directed toward giving as true an account as possible of the complete blood picture occurring not in the normal subject, but in the average ambulant patient seeking medical advice. Further, it was hoped that it would also appear whether or not there was a seasonal or other rhythmic variation observable in time, affecting any or all of the constituents of the blood examined. Because of the nature of the problem, a time interval of two years was chosen, the dividing unit in each case being the month. In the charts the number of cases will be found on the abscissal line just above the respective month.

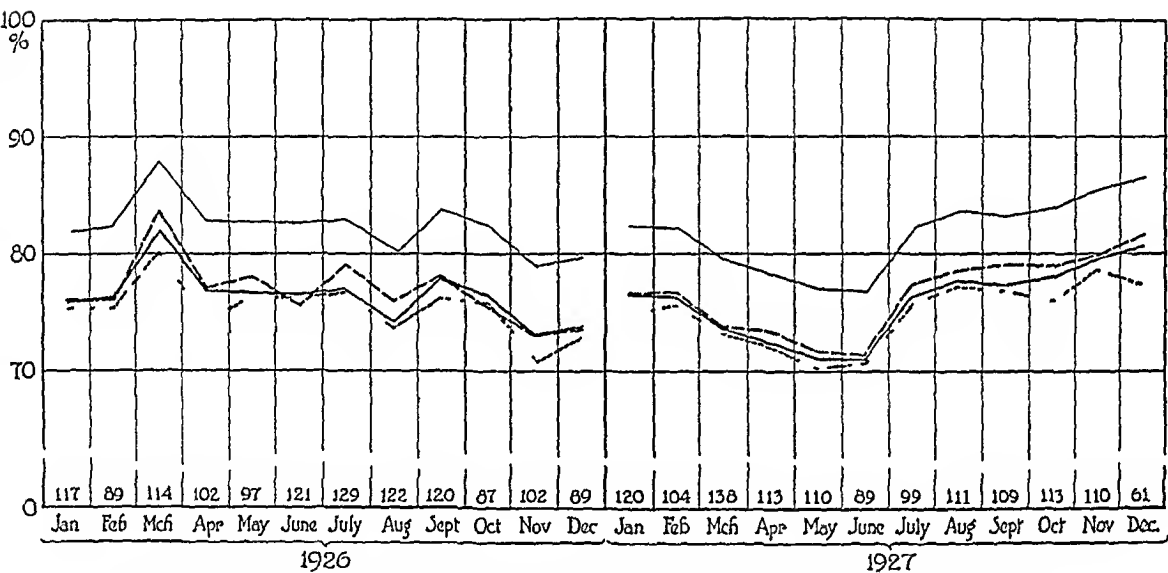


Chart 1—Mean (solid line), median (dash line) and mode (dotted line) for hemoglobin. The mean range was between 71.0 and 82.1 per cent.

In general, the examinations were made from two to three hours after breakfast, on an empty stomach, between 11 a. m. and 2 p. m. Throughout the series no more than three observers were concerned, all competent and all trained by the same person. A Dare hemoglobinometer was used in estimating hemoglobin values, and the Burke counting chamber with respective pipets was employed for determinations of red blood cells and leukocytes. Differential counts were made in all cases from slides colored with Wright's stain, and 200 cells were counted.

The Dare instrument used reads between 90 and 95 per cent for red blood cell values of 5,000,000 per cubic millimeter. On a scale of 100 per cent this means that the observed readings fall 6 points low. Chart 1 shows the degree of variation obtained. The arithmetical mean is seen here to fall between the median, which usually lies from 0.5 to

3 per cent above it, and the mode, lying somewhat less than that below it. The narrow, unbroken line running parallel to the mean and 6 points above it represents the theoretical hemoglobin value in these cases on the basis of a 100 per cent reading for 5,000,000 red blood cells. The mean range throughout the two years is practically 10 per cent. Two interesting features emerge clearly from the graph. The first is the low average for hemoglobin encountered, actually 76 per cent, and on the corrected scale only 81 per cent. Such figures do not, of course, signify anemia even though they are somewhat low. The next interesting thing is the observed difference in the readings of the mean, median and mode. Estimation of probable errors establishes the recorded differences as

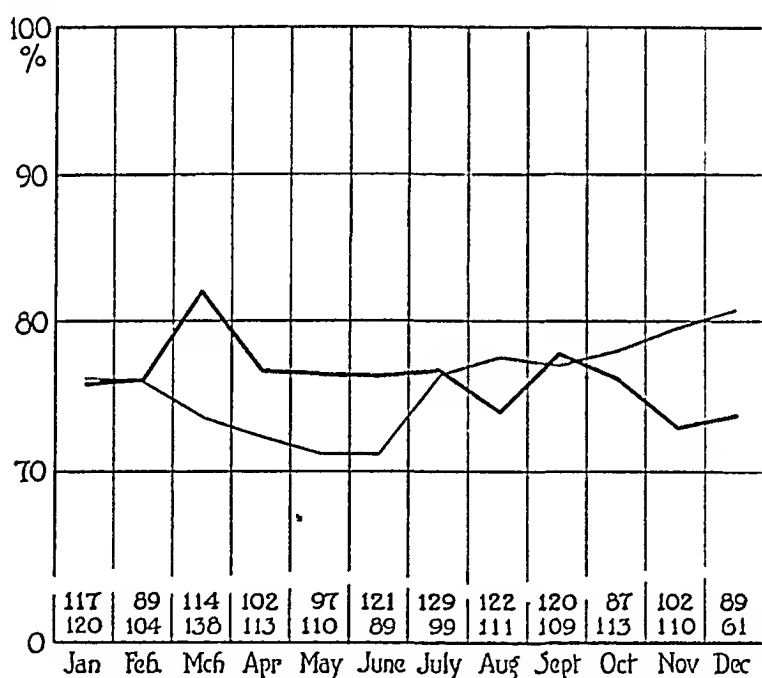


Chart 2—The 1926 (heavier line) and 1927 (lighter line) means for hemoglobin

significant. Chart 2 is a visual portrayal of the mean variation curves throughout the two years. It is at once apparent that no similarity of variation obtains in relation to the monthly time interval.

What has been said of the hemoglobin values applies with equal point to the erythrocytes. Chart 3 represents the observed variation of these. All of the readings lie below the accepted normal figure for men, and in every month but one they are under 4,500,000. Here, too, the difference in the three constants is brought out significantly in May, 1926, when an interval of almost 500,000 separates the mode and the median. The subjoined tables of probability of error again establish the differences as real. Chart 4 shows that there is no rhythmic variation present from month to month.

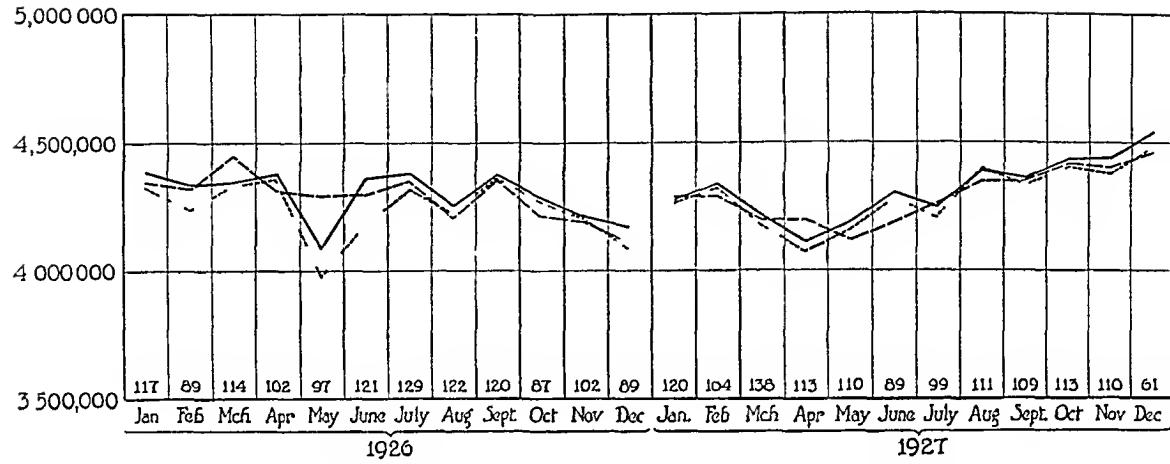


Chart 3—Mean (solid line), median (dash line) and mode (dotted line) for red blood cells The mean range was between 4,080,000 and 4,540,000

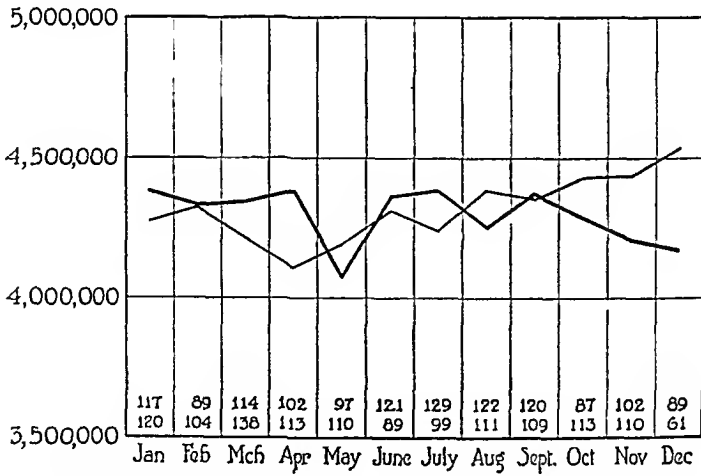


Chart 4—The 1926 (heavier line) and 1927 (lighter line) means for red blood cells

The extreme lability of myeloid function makes any total leukocytic variation subject to much conditional interpretation. Thus the daily leukocyte count has been shown to change with the hours. Ellermann and Erlandsen demonstrated a variation of from 7,400 to 10,000 white cells from 6 a. m. to 7 p. m., while Shaw held that there are two leukocytic tides during the twenty-four hours, both reaching their flood soon after noon and midnight. He doubted the existence of digestive leukocytosis, since his curves were independent of food, exercise and sleep. In chart 5, the mean range is from 7,280 to 9,060 for the two years. Here also the arithmetical mean presents a high figure and the median a low one, while the mode falls between the two. The average of the

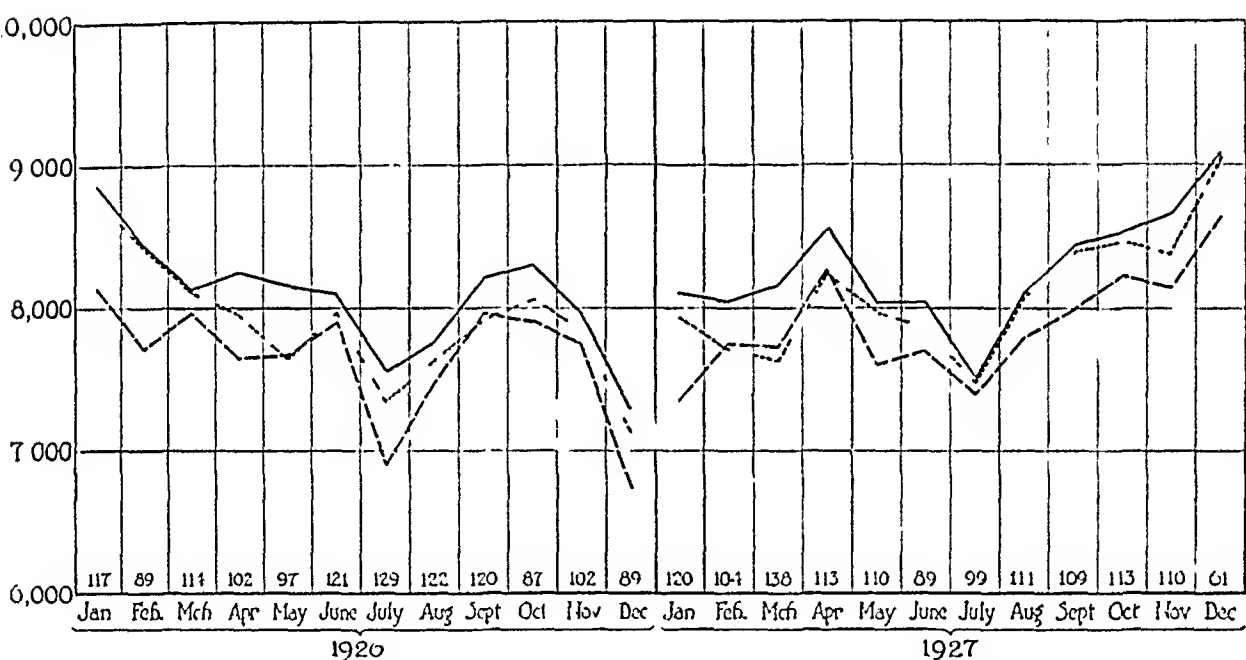


Chart 5—Mean (solid line), median (dash line) and mode (dotted line) for leukocytes. The mean range was between 7,280 and 9,060.

arithmetical mean over two years is established at 8,160 cells, or somewhat higher than the usual normal value. This tendency to lie above rather than below the normal value may bear some relation to mild chronic infection, a question more thoroughly considered later. Chart 6 shows that there is, in fact, a partial symmetry of variation in the two years. From March to October the curves follow one another rather closely, an interesting circumstance. On the other hand, the months of November and December show a wide difference, the meaning of which at present remains unclear.

The differential leukocyte values are here recorded only as two large groups: the polymorphonuclear elements and a second group termed lymphoid cells. Under the latter heading are included small and large

lymphocytes as well as the cells at present classified as monocytes. This was done for two reasons. 1. Wright's stain was used, and with this stain the differentiation between the large lymphocyte and monocyte is at best not always easy. The stain of choice would have been a modified Giemsa, which was not used in the laboratory throughout the period of observation. 2. The derivation and classification of the monocyte is at this time the subject of much discussion among hematologists, and for statistical purposes errors of morphologic classification were sedulously avoided. Briefly, the derivation of the monocyte has champions for three different points of origin. Naegeli¹ held to their myeloid origin, Bergel² to their lymphoid origin and Schilling³ to their origin from the

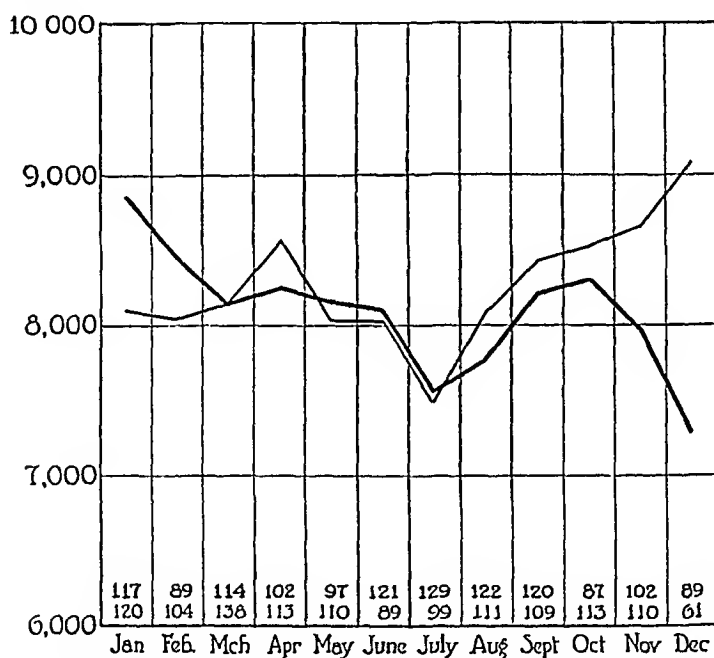


Chart 6—The 1926 (heavier line) and 1927 (lighter line) means for leukocytes

reticulo-endothelial cells. Finally, Kiyono⁴ and Mosczytz⁵ felt that they may be derived from all three. These considerations led to the adoption of the term lymphoid as covering, in the main, the large mononuclear cell, the transitional cell and the very large lymphocyte. It will be found that the recorded percentage of these, taken together with

1 Naegeli, O. *Blutkrankheiten und Blutdiagnostik*, Berlin, Julius Springer, 1923.

2 Bergel, S. *Die Lymphozytose*, Berlin, Julius Springer, 1921.

3 Schilling, V. *Das Blutbild und seine klinische Verwertung*, Jena, Gustav Fischer, 1926.

4 Kiyono, K. *Die vitale Karminspeicherung*, Jena, Gustav Fischer, 1924.

5 Mosczytz, N. *Ztschr f klin Med* **106** 582, 1927.

that of the polymorphonuclear cells, roughly averages 97. The remaining percentage represents cosmophils, which have not been graphically shown. Naegeli put the normal percentage of lymphocytes at from 20 to 25, of polymorphonuclears at from 65 to 70, and of monocytes at from 6 to 8. Schilling raised the normal lymphocytic variation to 35 per cent, while Egorov⁶ found the normal value in Moscow to be 37.6 per cent. The present series shows an arithmetical mean average for lymphoid cells of 37.9 per cent, as recorded in chart 7. The present average for polymorphonuclears is 59.8 per cent, which varies sharply from Egorov's value of 49.7 per cent or Schilling's of 67 per cent. The

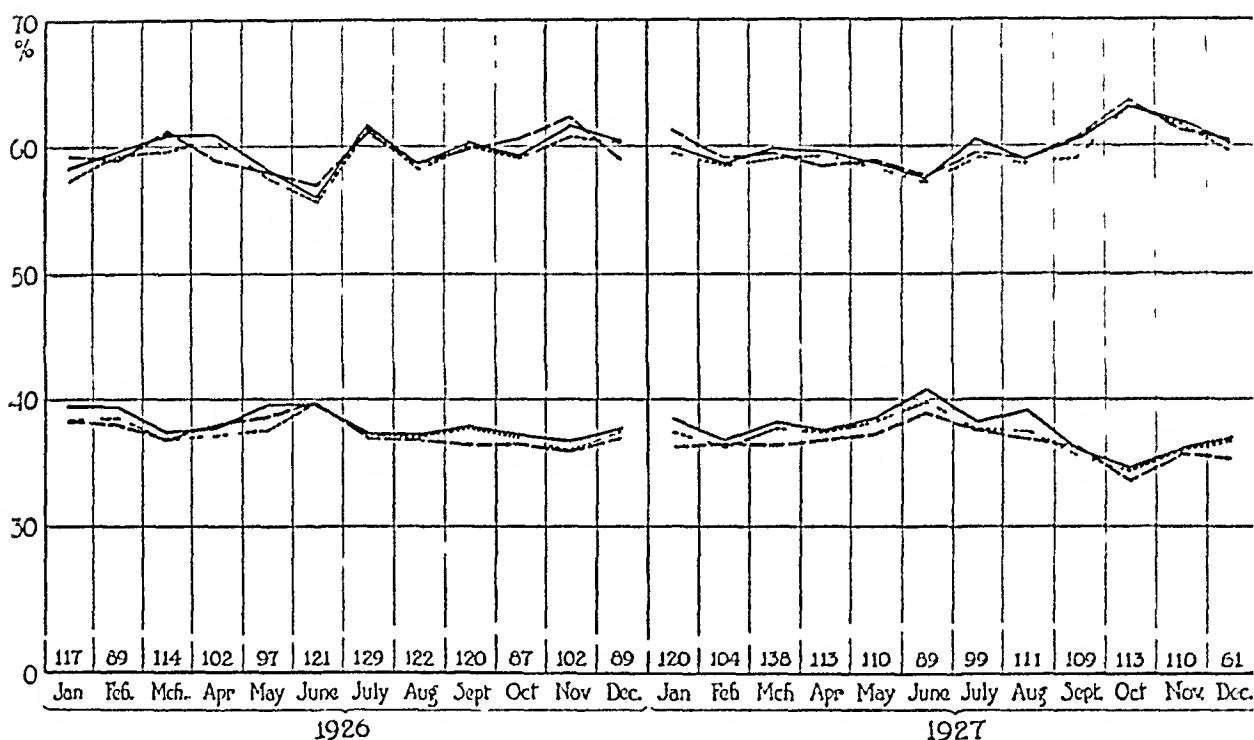


Chart 7—Mean (solid line), median (dash line) and mode (dotted line) for polymorphonuclears (upper group) and lymphoid cells (lower group). The mean range for polymorphonuclears was between 56.0 and 63.2 per cent, for lymphoid cells, between 34.6 and 40.8 per cent.

difference may be accounted for by geographic variation and different classification. Egorov's lymphocyte percentage, established in 1924, agrees with the present lymphoid average, the difference in the polymorphonuclear percentage indicating principally a variation in monocytes. Taken in conjunction with the polymorphonuclear value, one inclines to the belief that the lymphoid percentage here shown is high. The mean range is between 34.6 and 40.8 per cent. Both Arneth⁷ and

⁶ Egorov. *Ztschr. f. klin. Med.* **100**:485, 1924, *Therap. Arch.*, 1924, vol. 2.

⁷ Arneth. *J. Die qualitative Blutlehre*. Leipzig: W. Klinkhardt, 1920.

Schilling showed that a moderate lymphocytosis occurs in chronic infections, in the postinfective stages of many maladies and in various types of intoxication. This response is interpreted as a successful reticulo-endothelial defense against infection, the holding in check, as it were, of the progress of infection. This point of view seems to be borne out in the present analysis. As stated, many of these patients presented chronic focal infection of one sort or another, many also presented intoxications of postfebrile or other origin. The behavior of the polymorphonuclears is, of course, complementary to that of the lymphoid

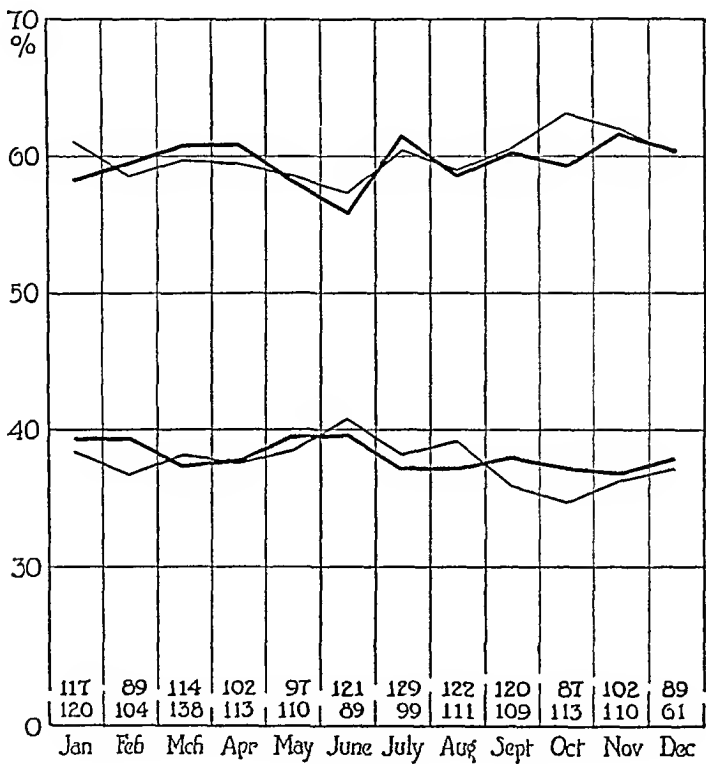


Chart 8.—The upper curves show the 1926 mean (heavier line) and 1927 mean (lighter line) for polymorphonuclears, the lower curves the 1926 and 1927 means for lymphoid cells. Two hundred cells were counted.

cells. In chart 8 a remarkable similar variation is observed over the two-year period with reference to these cells. Thus, May and June of both years show a high peak of lymphoid response, with a gradual declination throughout the rest of the year, while the reverse picture is true of the polymorphonuclear cells. The number of patients examined and the range of variation observed (6 per cent) make one feel that perhaps the obtained evidence of similar variation has some significance. A further study of the coefficients of variation may strengthen this view.

Chart 9 portrays the arithmetical mean averages, together with the probable errors of these averages, for the five elements investigated. For 2,562 cases they show a hemoglobin value of 76.1 per cent (81 per cent on a 100 per cent basis), a red blood cell count of 4,140,000 and a leukocyte count of 8,160.

The differential blood picture shows an average of 59.8 per cent polymorphonuclear cells, 37.9 per cent lymphoid cells and 2.3 per cent eosinophils and basophils.

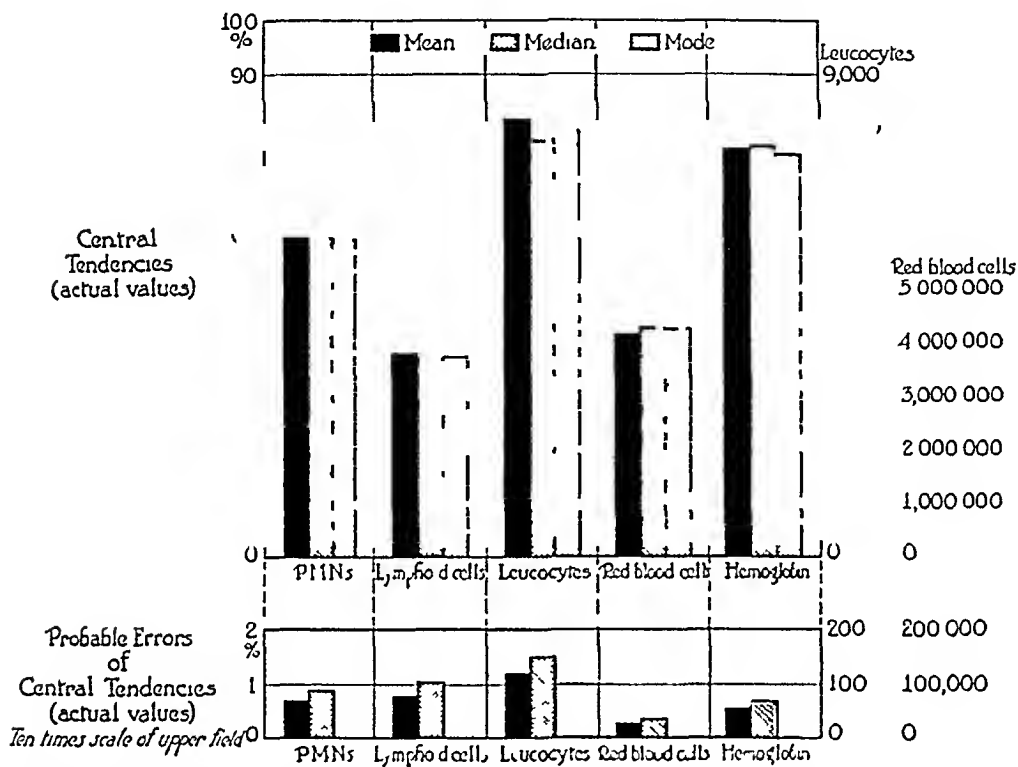


Chart 9—Arithmetical mean averages, with probable error, for polymorphonuclears (PMN's), lymphoid cells, leukocytes, red blood cells and hemoglobin

CONCLUSIONS

- 1 The three accepted constants of variation differ significantly when applied to complete examinations of the blood
- 2 For data of this kind, the arithmetical mean is a reliable constant
- 3 The hemoglobin and erythrocyte values in this group are definitely below normal
- 4 The total leukocyte count is perhaps slightly above normal
- 5 The percentage of lymphoid cells is above normal, probably because of chronic mild infections and intoxications
- 6 There is presumably a significant similar variation, month by month, among polymorphonuclear and lymphoid cells throughout a period of two years

TABLE 1—*Constants Determined for Hemoglobin*

Month, 1926	Mean	Median	Mode	Standard Deviation	Coefficient of Variation, per Cent
January	75.8	76.0	75.26	7.57	9.98
February	76.2	76.0	75.46	8.04	10.5
March	82.1	83.6	80.04	10.20	12.5
April	76.7	76.9	74.16	9.17	12.0
May	76.5	77.8	76.43	9.9	12.9
June	76.4	75.6	76.21	8.06	10.5
July	76.9	79.0	76.77	8.82	11.5
August	74.0	75.9	73.58	9.184	12.4
September	77.8	78.0	76.28	9.37	12.0
October	76.5	75.5	75.64	7.59	9.92
November	73.0	73.0	70.72	10.26	13.9
December	73.7	73.5	72.92	8.52	11.8
1927					
January	76.3	76.4	74.87	9.40	12.3
February	76.2	76.5	75.75	8.04	10.5
March	73.5	73.7	73.34	8.90	12.1
April	72.4	73.4	72.08	5.68	9.88
May	71.0	71.5	70.18	8.6	12.1
June	71.0	71.3	70.62	7.35	10.3
July	76.2	77.4	75.84	7.15	9.39
August	77.6	78.7	77.35	5.96	7.68
September	77.2	79.2	77.1	8.21	10.7
October	78.0	79.0	75.94	7.72	9.9
November	79.7	79.9	78.59	6.42	8.06
December	80.7	81.6	77.36	7.21	8.93

TABLE 2—*Constants Determined for Erythrocytes*

Month 1926	Mean	Median	Mode	Standard Deviation	Coefficient of Variation, per Cent
January	4,390,000	4,350,000	4,341,000	415,200	9.4
February	4,340,000	4,330,000	4,238,000	352,200	8.11
March	4,350,000	4,450,000	4,342,920	416,000	9.562
April	4,380,800	4,320,000	4,361,820	408,000	9.312
May	4,080,000	4,290,000	3,978,000	457,900	11.2
June	4,360,000	4,300,000	4,194,000	346,000	7.93
July	4,390,000	4,360,000	4,322,000	461,000	10.5
August	4,250,000	4,210,000	4,211,000	411,000	9.68
September	4,380,000	4,350,000	4,377,000	385,000	8.79
October	4,290,000	4,210,000	4,286,000	347,000	8.1
November	4,210,000	4,190,000	4,205,000	340,000	8.09
December	4,170,000	4,110,000	4,094,000	447,000	10.7
1927					
January	4,270,000	4,280,000	4,269,000	393,000	9.21
February	4,330,000	4,280,000	4,325,000	423,000	9.77
March	4,220,000	4,200,000	4,175,720	490,000	11.61
April	4,120,000	4,200,000	4,071,780	480,000	11.65
May	4,180,000	4,120,000	4,156,000	385,000	9.22
June	4,310,000	4,180,000	4,292,000	386,000	8.95
July	4,240,000	4,260,000	4,205,000	452,000	10.7
August	4,390,000	4,350,000	4,391,000	243,200	5.54
September	4,370,000	4,360,000	4,343,000	389,000	8.91
October	4,430,000	4,420,000	4,415,000	424,000	9.79
November	4,440,000	4,410,000	4,388,000	343,000	7.75
December	4,540,000	4,460,000	4,480,000	346,000	7.63

TABLE 3—*Constants Determined for Leukocytes*

Month, 1926	Mean	Median	Mode	Standard Deviation	Coefficient of Variation, per Cent
January	8,860	8,140	8,773	2,250	25.4
February	8,440	7,740	8,432	1,980	23.5
March	8,120	7,970	8,104	2,440	30.1
April	8,270	7,640	7,948	2,110	25.5
May	8,150	7,660	7,634	2,100	25.8
June	8,110	7,900	7,962	1,840	22.7
July	7,560	6,900	7,346	2,170	28.7
August	7,750	7,480	7,618	2,000	25.9
September	8,200	7,960	7,911	1,760	21.5
October	8,300	7,900	8,049	1,890	22.8
November	7,970	7,760	7,821	1,870	23.4
December	7,280	6,720	7,160	1,320	20.9
1927					
January	8,110	7,350	7,927	2,210	26.0
February	8,040	7,750	7,704	1,930	24.1
March	8,150	7,720	7,622	2,070	25.3
April	8,560	8,260	8,250	2,140	25.0
May	8,030	7,600	7,981	1,900	23.7
June	8,030	7,700	7,843	1,830	22.8
July	7,500	7,380	7,480	1,360	18.2
August	8,110	7,780	8,074	1,744	21.5
September	8,430	7,980	8,396	1,344	16.0
October	8,510	8,209	8,450	1,328	15.6
November	8,650	8,130	8,383	1,784	20.6
December	9,060	8,620	9,050	1,692	18.7

TABLE 4—*Constants Determined for Polymorphonuclears*

Month, 1926	Mean	Median	Mode	Standard Deviation	Coefficient of Variation, per Cent
January	58.4	59.4	57.44	12.40	21.0
February	59.7	59.0	59.49	10.09	16.9
March	60.9	61.1	59.73	11.54	18.9
April	60.9	58.9	60.53	9.13	15.0
May	58.3	58.1	57.58	12.80	21.9
June	56.0	57.0	55.53	9.32	16.6
July	61.6	61.1	61.34	10.51	17.1
August	48.7	58.7	58.24	10.48	17.9
September	60.2	59.8	59.89	10.15	16.9
October	59.4	60.7	59.34	12.20	20.5
November	61.5	62.3	60.94	10.36	16.9
December	60.3	59.0	60.27	9.25	15.3
1927					
January	60.0	61.3	59.67	8.69	19.6
February	58.6	59.0	58.52	10.20	17.6
March	59.9	59.7	59.01	11.12	18.6
April	59.5	58.5	59.36	11.19	18.8
May	58.6	58.7	58.49	10.69	18.3
June	57.5	57.6	57.30	13.04	22.5
July	60.0	59.5	59.01	9.22	15.4
August	59.0	59.0	58.90	9.58	16.3
September	60.5	60.7	59.20	9.65	16.0
October	63.2	62.8	62.82	9.64	15.2
November	61.9	61.2	61.66	6.68	10.7
December	60.1	60.3	59.62	9.17	15.2

TABLE 5—*Constants Determined for Lymphoid Cells*

Month, 1926	Mean	Median	Mode	Standard Deviation	Coefficient of Variation, per Cent
January	39.6	38.3	38.3	12.7	32.0
February	39.6	38.0	38.5	12.54	31.7
March	37.4	36.9	36.9	8.4	28.3
April	37.8	38.0	37.1	10.68	28.3
May	39.7	38.7	37.57	12.20	30.5
June	39.7	39.8	39.7	10.21	25.7
July	37.3	37.0	37.2	9.71	26.1
August	37.1	36.9	37.0	10.80	29.1
September	37.8	36.4	37.7	11.58	30.6
October	37.2	36.4	37.0	5.17	25.6
November	36.7	36.0	36.0	9.20	25.1
December	37.8	37.0	37.6	9.80	25.9
1927					
January	38.5	36.2	37.3	12.76	33.0
February	36.8	36.6	36.3	8.29	22.5
March	38.3	36.4	37.8	9.56	24.9
April	37.6	36.9	37.4	11.16	29.7
May	38.7	37.4	38.4	10.60	27.4
June	40.8	39.0	39.9	13.66	33.5
July	38.3	37.7	37.7	8.05	21.0
August	39.2	37.0	37.3	10.49	26.8
September	36.1	36.2	35.6	8.56	23.7
October	34.6	33.6	34.4	7.77	22.7
November	36.2	35.9	36.1	6.72	18.5
December	37.1	35.3	36.9	8.92	24.1

TABLE 6—*Probable Error of Mean and Median Determined for Hemoglobin*

Month, 1926	Mean	Probable Error, per Cent	Median	Probable Error, per Cent
January	75.8	0.4719	76.0	0.5914
February	76.2	0.5716	76.0	0.7165
March	82.1	0.6443	83.6	0.8080
April	76.7	0.6155	76.9	0.7717
May	76.5	0.6708	77.8	0.8408
June	76.4	0.4968	75.6	0.7840
July	76.9	0.5260	79.0	0.6593
August	74.0	0.5535	75.9	0.7000
September	77.8	0.5723	78.0	0.7170
October	76.5	0.5723	75.5	0.7170
November	73.0	0.7507	73.0	0.9410
December	73.7	0.6193	73.5	0.9120
1927				
January	76.3	0.5810	76.4	0.7280
February	76.2	0.5317	76.5	0.6660
March	73.5	0.5110	73.7	0.6400
April	72.4	0.3654	73.4	0.4580
May	71.0	0.5553	71.5	0.6960
June	71.0	0.5227	71.3	0.6550
July	76.2	0.4850	77.4	0.6070
August	77.6	0.3213	78.7	0.4030
September	77.2	0.5284	79.2	0.6620
October	78.0	0.5960	79.0	0.6220
November	79.7	0.4112	79.9	0.5150
December	80.7	0.6223	81.6	0.7800

TABLE 7—*Probable Error of Mean and Median Determined for Erythrocytes*

Month, 1926	Mean	Probable Error, per Cent	Median	Probable Error, per Cent
January	4,390,000	0 2600	4,350,000	0 3250
February	4,340,000	0 2532	4,330,000	0 3170
March	4,350,000	0 3060	4,450,000	0 3830
April	4,380,000	0 2720	4,320,000	0 3410
May	4,080,000	0 3120	4,290,000	0 3910
June	4,360,000	0 2130	4,300,000	0 2670
July	4,390,000	0 2762	4,360,000	0 3460
August	4,250,000	0 2435	4,210,000	0 3120
September	4,380,000	0 2372	4,350,000	0 2970
October	4,290,000	0 2603	4,210,000	0 3260
November	4,210,000	0 2270	4,190,000	0 2850
December	4,170,000	0 3193	4,110,000	0 4000
1927				
January	4,270,000	0 2422	4,280,000	0 3040
February	4,330,000	0 2770	4,280,000	0 3470
March	4,220,000	0 2750	4,200,000	0 3450
April	4,120,000	0 3200	4,200,000	0 4010
May	4,180,000	0 2477	4,120,000	0 3170
June	4,310,000	0 2761	4,180,000	0 3460
July	4,240,000	0 3061	4,260,000	0 3837
August	4,390,000	0 1523	4,350,000	0 1906
September	4,370,000	0 2514	4,360,000	0 3150
October	4,430,000	0 2777	4,420,000	0 3480
November	4,440,000	0 2199	4,388,000	0 2760
December	4,540,000	0 2999	4,460,000	0 3750

TABLE 8—*Probable Error of Mean and Median Determined for Leukocytes*

Month, 1926	Mean	Probable Error, per Cent	Median	Probable Error, per Cent
January	8,860	1 418	8,140	1 780
February	8,440	1 402	7,740	1 760
March	8,120	1 536	7,970	1 930
April	8,270	1 425	7,640	1 790
May	8,150	1 441	7,660	1 810
June	8,110	1 133	7,900	1 420
July	7,560	1 309	6,900	1 640
August	7,750	1 224	7,480	1 530
September	8,200	1 084	7,960	1 360
October	8,300	1 419	7,900	1 410
November	7,970	1 253	7,760	1 570
December	7,280	1 096	6,720	1 370
1927				
January	8,110	1 300	7,350	1 630
February	8,040	1 280	7,750	1 610
March	8,150	1 186	7,720	1 490
April	8,560	1 357	8,260	1 700
May	8,030	1 210	7,600	1 520
June	8,030	1 308	7,700	1 640
July	7,500	0 9238	7,380	1 160
August	8,110	1 117	7,780	1 400
September	8,430	0 8018	7,980	1 000
October	8,510	0 840	8,209	1 983
November	8,650	1 147	8,130	1 440
December	9,060	1 461	8,620	1 830

TABLE 9—*Probable Error of Mean and Median Determined for Polymorphonuclears*

Month, 1926	Mean	Probable Error, per Cent	Median	Probable Error, per Cent
January	59.4	0.7735	59.4	0.9700
February	59.7	0.7215	59.0	0.9040
March	60.9	0.7290	61.1	0.8333
April	60.9	0.6088	58.9	0.7630
May	58.3	0.6250	58.1	0.7836
June	56.0	0.6088	57.0	0.7580
July	61.6	0.6388	61.1	0.8010
August	58.7	0.6401	58.7	0.8020
September	60.2	0.6252	59.8	0.7840
October	59.4	0.7008	60.7	0.8780
November	61.5	0.6920	62.3	0.8670
December	60.3	0.6588	59.0	0.8350
1927				
January	60.0	0.7280	61.3	0.9120
February	58.6	0.6830	59.0	0.8560
March	59.9	0.6362	59.7	0.7970
April	59.5	0.7128	58.5	0.8940
May	58.6	0.6878	58.7	0.8620
June	57.5	0.9430	57.6	1.180
July	60.0	0.6285	59.5	0.7880
August	59.0	0.6083	59.0	0.7620
September	60.5	0.6177	60.7	0.7740
October	63.2	0.5436	62.8	0.6810
November	61.9	0.3995	61.2	0.5010
December	60.1	0.7922	60.3	0.9930

TABLE 10—*Probable Error of Mean and Median Determined for Lymphoid Cells*

Month 1926	Mean	Probable Error, per Cent	Median	Probable Error, per Cent
January	39.6	0.8708	38.3	1.090
February	39.6	0.8870	38.0	1.110
March	37.4	0.5255	36.9	0.6620
April	37.8	0.7088	38.0	0.8880
May	39.7	0.8305	38.7	1.040
June	39.7	0.6888	39.8	0.7950
July	37.3	0.5810	37.0	0.7280
August	37.1	0.6610	36.9	0.8290
September	37.8	0.7190	36.4	0.9022
October	37.2	0.7187	36.4	0.7100
November	36.7	0.6184	36.0	0.7690
December	37.8	0.7100	37.0	0.8900
1927				
January	38.5	0.8353	36.2	1.050
February	36.8	0.5505	36.6	0.7400
March	38.3	0.5490	36.4	0.6680
April	37.6	0.7103	36.9	0.8910
May	38.7	0.6845	37.4	0.8580
June	40.8	0.9766	39.0	1.220
July	38.3	0.3307	37.7	0.4150
August	39.2	0.5309	37.0	0.6600
September	36.1	0.5530	36.2	0.6950
October	34.6	0.4993	33.6	0.6260
November	36.2	0.4120	35.9	0.5200
December	37.1	0.7707	35.3	0.9660

TABLE 11—*Determination of Constants*

	Z	X	ZX	ZX(2)	ZX(3)	ZX(4)
20	2	1	2	2	2	2
24	8	2	16	32	64	128
28	12	3	36	108	324	972
32	13	4	52	208	832	3,328
36	22	5	110	550	2,750	13,750
40	11	6	66	396	2,376	14,256
44	12	7	84	588	4,116	28,812
48	11	8	88	704	5,632	47,056
52	11	9	99	891	8,019	72,171
56	1	10	10	100	1,000	10,000
60	4	11	44	484	5,324	58,564
64	5	12	60	720	8,640	103,680
68	3	13	39	507	6,591	85,683
76	1	15	15	225	3,375	50,625
84	1	17	17	289	4,913	82,521

 $S(Z) \ 119$
 $S(ZX) \ 738$
 $S(ZX)^2 \ 5,801$
 $S(ZX)^3 \ 53,938$
 $S(ZX)^4 \ 560,543$

$$V_1 = \frac{S(ZX)}{S(Z)} = 6.20$$

$$V_3 = \frac{S(ZX)^3}{S(Z)} = 453.4$$

$$V_2 = \frac{S(ZX)^2}{S(Z)} = 48.7$$

$$V_4 = \frac{S(ZX)^4}{S(Z)} = 4710.4$$

$$\pi_1 = V_2 - V_1^2 = 10.26$$

$$\mu_{u2} = \pi_2 - \frac{1}{2}\pi_1 (= 0.08333) = 10.18$$

$$a = \sqrt{\mu_{u2}} = 3.19$$

$$\text{Standard deviation} = 4 \times 3.19 = 12.76$$

$$\text{Probable error of mean} = X_1 \text{ (where } X = 0.6744898/N) \times S.D. = 0.8353$$

$$\pi_3 = V_3 - 3V_1V_2 + 2V_1^3 = 13.062$$

$$\pi_4 = V_4 - 4V_1V_3 + 6V_1^2V_2 - 3V_1^4 = 326.2477$$

$$\mu_{u3} = \pi_3 = 13.062$$

$$\mu_{u4} = \pi_4 - \frac{1}{2}\pi_2 + \frac{7}{240} (= 0.029167) = 320.573367$$

$$B_1 = \frac{\mu_{u3}^2}{\mu_{u2}^3} = 0.11487$$

$$B_2 = \frac{\mu_{u4}}{\mu_{u2}^3} = 2.4635$$

$$X = \frac{\sqrt{B_1}(B_2 + 3)}{2(5B_2 - 6B_1 - 9)} =$$

$$d = X \times a = 1.19$$

$$\text{Mode} = \text{mean} - d = 37.3$$

$$\text{Coefficient of variation} = \frac{S.D.}{\text{mean}} \times 100 = 33 \text{ per cent}$$

Lymphocytes, January, 1927

Estimation of mode, probable error of mean, standard deviation, and coefficient of variation of the mean in per cent

$$\text{Estimation of median} \frac{0.5}{11} \times 4 \text{ (the class interval)} + 36 = 36.2, \text{ median}$$

EFFECT OF INTRATHORACIC PRESSURE ON ARTERIAL TENSION*

ELI GRIMES, M D

DES MOINES, IOWA

When the intrathoracic pressure is raised above that of the great extrathoracic veins which pass the blood back to the chest, definite changes based on elementary physical principles follow

If a person shuts off the outlet of air by closing the larynx or nose and lips and makes a forced expiratory effort (blowing), the intrathoracic pressure rises, and the blood cannot flow into the chest, hence, the right side of the heart does not fill, the blood is soon pumped out of the lungs, and the left ventricle likewise becomes empty, arterial circulation is momentarily suspended, and the systolic blood pressure falls to zero

EXPERIMENTAL PROCEDURE

Experiment 1—Place within the lips a tube connected with a manometer and make a blowing effort till the manometer registers from 40 to 60. If this can be held for a sufficient length of time there follows a general venous engorgement, the subject becomes cyanotic, the veins stand out, there is a sense of giddiness, and the normal respirations must be begun. At this point the systolic pressure is zero, but after three or four respirations it rises from 50 to 150 above the patient's normal pressure. The explanation of this is evident. The increased intrathoracic pressure shuts the blood out of the heart—the zero phase of pressure—and then, when the intrathoracic pressure is released, the greatly distended veins suddenly empty into the right auricle, the heart is overloaded, the increased volume of blood overdistends the arterial system, and the pressure rises. The rise of pressure depends on the amount of blood, the elasticity of the arteries and the contractile force of the heart. Herein lies the clinical value of this test, namely, the elasticity of the arteries.

It is a principle in physiology that the size of the heart is that of the heart tissues plus the contained blood, therefore, it is possible

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When these original observations were begun in 1910, there was no literature on the subject. The line of investigation was explained to the medical directors of various life insurance companies. Soon there was published an account of the technic, but the interpretation was not in accord with the facts. No account has been taken of the literature which has since been published.

to measure the relative amount of blood in the heart by determining the change in size. If a silhouette of the heart is taken when the systolic pressure is zero, it is found to be from 25 to 35 per cent smaller than when the respirations are regular, and if another silhouette is taken when the pressure is elevated at the time respirations are resumed, it will be found to be from 35 to 50 per cent larger than under usual conditions.

In the accompanying table, the measurements of the silhouettes of the heart cover a complete cycle of respiration. The size of the heart with the patient at rest is designated as 10.

Blood Pressure and Size of the Heart in Ten Subjects at Rest, on Producing and on Releasing Intrathoracic Pressure

Intrathoracic Pressure Normal Blood Pressure	Intrathoracic Pressure 50		On Releasing Intrathoracic Pressure	
	Blood Pressure	Heart Measurements	Blood Pressure	Heart Measurements
140	0	7	170	17
80	0		90	
130	0		180	
70	0	8	90	17
125	0		200	
80	0	6	100	18
135	0		240	
75	0	6	120	18
145	0	8	175	
85	0		80	14
145	0	7	160	
75	0		80	15
135	0	7	150	
80	0		80	16
140	0		160	
80	0	6	90	15
145	0		155	
85	0	8	90	14
130	0		140	
80	0	7	80	15

The observation that the heart undergoes the same changes in size with a low rebound as it does with a high rebound led to the conclusion that the change in pressure is not due to the condition of the heart or to the volume of blood, therefore, it is due to arterial differences, and the only arterial condition which can cause a variation of pressure is that of elasticity. Other conditions being constant, the elevation in pressure is in inverse ratio to the elasticity of the arteries. Therefore, the respiratory rebound is a measure of the elasticity of the arteries.

PHYSIOLOGIC CONSIDERATIONS

The intrathoracic pressure is a natural accompaniment of hard muscular effort. When a heavy weight is lifted, a heavy blow is struck or a maximum muscular effort of any kind is made, the breath is forcibly held to a point of "getting black in the face." This getting

black in the face is due to the fact that the increased intrathoracic pressure prevents the return of the blood to the chest. The amount of blood in the chest is less than that required for hard muscular work if the breath is held reflexly. Observe a man carrying a heavy weight up a flight of steps, note the infrequency of respirations, his cyanosis and his distended veins, it is evident that he is using more blood than is contained in his chest, or that it returns against the greatly increased intrathoracic pressure. This being the case, there must be an extra-thoracic supply of blood, and it can come only from the great vessels of the abdomen. Hence, the intra-abdominal pressure must be at all times as great as the intrathoracic pressure. Otherwise, there would be sudden shutting off of the blood reaching the heart, and prolonged maximum muscular effort would be impossible.

This physiologic deduction led to an investigation of the relation between the intra-abdominal and the intrathoracic pressure, and it was found that the intrathoracic pressure cannot be raised above the intra-abdominal. It is a physiologic necessity that the supply of blood cannot be abruptly shut off from the heart as would be the case if there was no supply outside the chest.

Experiment 2—A Baines bag fitted to the end of a small rectal tube is inserted high in the colon, 500 cc of air is injected into the bag, and the free end of the tube is attached to a manometer. If the subject has been properly prepared by colonic flushing, and if morphine has been administered to prevent peristalsis, the following results are obtained:

When the subject is at rest the intra-abdominal pressure remains near zero, with slight fluctuations, owing to movements of the viscera. When the intrathoracic pressure is raised by the expiratory test, the intra-abdominal pressure rises to the same level. With a manometer tube in the subject's mouth on expiratory effort, the same elevation is recorded by the manometer indicating intrathoracic pressure and the one indicating the intra-abdominal pressure. A laboring man fitted with a colon manometer, as described, recorded an intra-abdominal pressure of 60 when he lifted a 250 pound (114.3 Kg) weight. When he swung a 50 pound (22.7 Kg) sledge delivering driving blows on the ground, there was a sudden short rise each time he struck with his breath reflexly held. The intra-abdominal pressure reached as high as 110, demonstrating a terrific stress on the heart.

It was found that while breathing is carried on, the abdominal muscles by their contraction can bring the intra-abdominal pressure much above the intrathoracic, but by no means can the intrathoracic pressure be brought above the intra-abdominal. The important conclu-

sion was reached that the intrathoracic pressure never exceeds the intra-abdominal. This is an important point in the physiology of the distribution of the blood.

When the great volume of venous blood contained in the abdomen, with its liver and spleen and great veins, is considered in connection with the fact that raising the intra-abdominal pressure simultaneously with that of the chest causes marked changes, the inference was made that increasing the intra-abdominal pressure alone would likewise cause changes in the blood pressure. But since abdominal pressure alone would not diminish the supply of blood to the heart, there would be no fall in arterial tension, on the contrary, the supply of blood to the heart would be increased, and therefore, the arterial pressure would be increased. This was found to be the case.

Experiment 3—If during regular and normal breathing a person voluntarily contracts the abdominal muscles with all the effort possible there follows at once a marked rise in arterial tension. This rise in pressure is conditioned on the degree of effort, the physical type of the subject and the condition of the arteries.

There is a great difference in the degree of effort that different persons can make, as there is a strong tendency for the glottis to close reflexly during "straining," thus increasing the intrathoracic pressure.

Persons who showed a rebound of systolic pressure to 200 on performing the blowing test could raise the blood pressure 20 above the normal pressure when at rest by contracting the abdominal muscles alone. Those showing no abnormal respiratory rebound could not raise their arterial tension by abdominal effort, as a rule, but some whose rebound was normal, that is, not more than 50 above their normal pressure at rest, could raise their systolic pressure 10 points above the normal point at rest. It is therefore evident that the increase of systolic pressure due to abdominal straining is the result of the increased volume of blood that reaches the heart.

It was determined that the ability to increase the systolic pressure by abdominal effort depended on the condition of the arteries, but mainly on the musculature of the individual.

In studying the changes in arterial pressure due to the changing blood volume, an important observation was made on the effect of an increased respiratory rate. If a person is made to breathe rapidly and deeply for a period of from three to five minutes, his blood pressure falls. In normal persons, this fall is from 10 to 20 systolic and from 5 to 10 diastolic. In persons with hypertension, the fall is most striking. After doubling the rate of respiration for five minutes an individual with a systolic pressure of 200 and a diastolic of 110 had

a blood pressure of only 140 systolic and 80 diastolic. When normal breathing was resumed, the pressure rose rapidly to its regular high level.

In hypertension of long standing, that is, when it occurs in older persons, this phenomenon is less marked, but in young subjects, that is, when the high blood pressure is not of long standing, the fall is most marked.

In a series of ten patients from 40 to 45 years of age with blood pressures averaging 175 systolic and 105 diastolic, the average pressure became 150 systolic and 90 diastolic after the rate and depth of respiration were doubled for five minutes.

In 100 syphilitic patients with normal blood pressure and no cardiovascular changes in clinical evidence, 75 per cent gave a respiratory rebound averaging 175 for the group, as compared with an average of 15 per cent in nonsyphilitic persons. This is certainly in accord with the conception that syphilis is first and always a vascular disease.

The mechanism of apoplexy is demonstrated by the respiratory rebound. Apoplexy that comes on as the result of excessive muscular effort does not come on during the effort but after it. During hard muscular effort, the arterial pressure falls as the blood is held back in the venous system, but when effort ceases deep respirations ensue, the venous blood is released, the heart and arteries are overdistended, the pressure rises, and apoplexy is the result. Apoplexy is often caused by straining at defecation, but it does not come on during the effort of straining but afterward. I observed a man carry his wife, who had been injured in the street, up a flight of steps into the house and lay her on a couch. It was a terrific effort, as the wife weighed 160 pounds (72.6 Kg). After placing her on the couch, he took a few deep breaths, and had a sudden fatal stroke of apoplexy. This is the mechanism of apoplexy occurring in patients with low blood pressure and hardened arteries. Acute dilatation of the heart is thus caused on effort.

The observations here set forth were made in 1910, and were so reported to the Des Moines Medical Library Club (unpublished). At that time it was stated that the value of this test could be determined in a patient only after the lapse of many years—at least twenty. If a person with a normal pressure, as usually determined, shows a high pressure on expiratory effort indicating an inelastic condition of the arteries, time alone will tell if this inelastic condition is of clinical importance.

It was first necessary to determine what constitutes a normal and an abnormal rebound. After the test was applied to 1,000 persons, it was evident that an elevation of arterial tension not exceeding 25 was

the rule, so this was considered normal. Increases in pressure above that were found to be unusual, and were considered abnormal. It was possible to select a series of 100 persons from 40 to 45 years of age, who twenty years ago showed an abnormally high rebound. This series was checked with an equal number of persons of the same age who at the same time showed a normal rebound. At rest, the normal series had an arterial tension not exceeding 140 systolic, and a systolic rebound not exceeding 165. The abnormal series had an arterial tension when at rest not exceeding 140 systolic, with a rebound of 190 or more on expiratory effort. All of the cases were fully checked so as to exclude kidney disease and syphilis, as it was early noted that syphilitic subjects almost invariably gave an abnormally high rebound.

Of the 100 patients with a rebound to 165 or less, 88 are living and 12 died from the following causes: pneumonia, 4, acute rheumatic endocarditis, 1, nephrosis, 1, tuberculosis, 1, thrombophlebitis, 1, and myocarditis (infectious) 1, the cause of death in 3 was not determined. Of the 100 patients with a systolic rebound to 190 or more, 68 are living and 32 died from the following causes: apoplexy, 4, nephrosis, 12, angina pectoris, 4, myocarditis, 2, pneumonia, 2, influenza, 4, and dementia, 1, the cause of death in 3 was not determined.

The test has been applied to every patient with a lesion of the heart coming under observation. The series included progressive and stationary mitral lesions, acute and chronic myocarditis, rheumatic endocarditis—studied from the onset of symptoms until the fatal termination or until the lesions became stationary—lesions of the aortic valve and subacute bacterial endocarditis. In no case did the test indicate the condition of the heart as to structural changes or the degree of efficiency. While the test is seemingly a severe strain on the heart, in no case was there evidence of its being harmful. In cases of heart failure, the sense of air-hunger comes on so early in making the blowing test that it was necessary for breathing to be resumed before damage was done.

COMMENT

It has been observed that a forced expiratory effort made with the exit of air closed causes a drop in systolic pressure, that when the breathing is resumed there is a marked elevation in the pressure, and that the elevation so produced is usually not more than 25 above the individual's pressure at rest. This pressure was therefore considered normal. In some persons the pressure rises to 75 or more above the pressure at rest. Such rebounds were considered abnormal.

It was shown that the change in pressure was due to shutting off the supply of blood to the heart because of increased intrathoracic

pressure, thereby causing a drop in pressure, and that when normal respirations were begun the heart and arteries were suddenly overloaded by the blood that had been dammed back, thus causing a sudden high wave of arterial tension

It was observed that the intrathoracic pressure never exceeded the intra-abdominal, a fact which explains the physiology of the supply of blood to the heart during effort

It was demonstrated that an abdominal high wave of arterial pressure was due, not to the condition of the heart, but to the diminished elasticity of the arteries

A series of 100 patients with abnormally high rebound was checked with that of an equal number with a normal rebound. These two series were kept under observation for twenty years. The mortality in the series with a high rebound was 32 per cent in twenty years compared with a mortality of 12 per cent in the series with a normal rebound. The high mortality was due to vascular or renal failure.

CONCLUSIONS

The test is a positive measure of arterial elasticity, and is of definite clinical value.

A high respiratory rebound is the first indication of oncoming hypertension and of arterial fibrosis, with or without high pressure.

A person showing a high rebound should be intensively studied for syphilis and nephritis.

The test does not indicate the integrity of the heart, measure its efficiency or foretell its failure.

THE VALUE OF DETERMINATIONS OF THE IRON CONTENT OF WHOLE BLOOD^{*}

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That iron is a constant and important constituent of the hemoglobin of mammals has been recognized for many years, and in consequence it has played an important rôle in the treatment for anemias. Therefore, it is somewhat surprising to find so little evidence in the literature of studies of the blood iron. Although a few determinations of the iron content of the blood under varying conditions have been made, there has been little effort to utilize these figures as a means of distinguishing between the various types of anemia or to follow the changes that may occur in the hemoglobin during the course of treatment for anemia by means of iron or other substances.

The observations recorded in this paper were made particularly in order to determine another means of differentiating between the types of anemia and also to establish a satisfactory method of following the changes that may occur in the blood of an anemic person being treated with various substances. With this in mind, it seemed advisable to establish the normal figure for whole blood iron by determinations on the blood of a group of normal persons. Few determinations of whole blood iron have been recorded on normal human blood in recent years which are comparable to the figures here recorded.

METHOD AND PROCEDURE

Ten cubic centimeters of blood was withdrawn from a vein of the arm and placed in a test tube that had been previously prepared by evaporating to dryness therein 2 cc of a 16 per cent solution of sodium oxalate that contained no iron. Gentle tilting of the tube prevented clotting and the formation of air bubbles which occur with shaking. The amount of hemoglobin in the blood was usually estimated by Osgood and Haskins'¹ modification of Sahli's method, and a careful red blood

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1 Osgood, E E, and Haskins, H D. A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, *J Biol Chem* **57** 107, 1923

cell count was made, standardized pipets and counting chambers being used. Duplicate determinations were made of the iron contained in the whole blood by the colorimetric method suggested by Kennedy.² This method was chosen because the chemical principles involved appeared to be sound and because it is a sufficiently simple method to be of practical value in the average chemical laboratory. Kennedy pointed out that the principle advantages of this method over others that have been suggested are the use of perchloric acid as a means of digesting the blood more rapidly and the addition in like amount of all reagents both to the standard iron solution and to the "unknown" blood. In this way the reaction of both is kept the same, and any traces of iron that might be contained in the reagents used will appear in equal amounts in the standard as well as in the "unknown." It has been pointed out by Kennedy and confirmed by us that after the ferric thiocyanate color has been produced, the reading will be influenced both by heat and by delay in making the colorimetric reading. Therefore, it is necessary to maintain a fairly uniform temperature in the flask and also to prepare only a few specimens at a time for colorimetric reading. The presence of small amounts of phosphates does not affect the reading. Although it was possible to check the determinations for iron made by Kennedy's method and the iron content of normal blood was found to range within rather narrow normal limits, our observations suggested that the "normal" figures so obtained are lower than the true values. A discussion of this subject will be considered in a paper which will appear later.

The amount of iron in the whole blood is expressed in milligrams per hundred cubic centimeters of whole blood.

The Iron Index—By dividing the milligrams of iron per hundred cubic centimeters of blood by the number of red blood cells per hundred cubic centimeters of the same venous blood used in making the determination for iron, it is possible to know the amount of iron in the average individual red blood cell and therefore to compare the relative concentration of iron in the blood of different persons. As it was believed that such a determination would be of significance in differentiating between the types of anemia, a more practical calculation is suggested which would indicate roughly the same information. It is suggested that the figure so obtained be called the "iron index," and it may be calculated by dividing the number of milligrams of iron per hundred cubic centimeters of blood by the red blood cell count expressed in millions per cubic millimeter of venous blood. For example, a person having 4,700,000 red blood cells per cubic millimeter and 41 mg. of iron per hundred cubic centimeters of venous blood would have an iron index of $\frac{41.0}{4.70}$ or 87. This figure (the iron index) may be used in place of the color index in differentiating the anemias, and it is probably a more reliable figure than is the color index as generally calculated.

RESULTS

Normal Persons—It is difficult to compare the figures for whole blood iron which we have obtained with many of those that are available in the literature, owing to the fact that the earlier figures are generally recorded in terms of a given weight rather than volume of blood. The

² Kennedy, R. P. The Quantitative Determination of Iron in the Tissues, *J. Biol. Chem.* **74** 385, 1927.

methods of determining the blood iron have varied considerably, so that the same method has rarely been followed by any two observers

Probably the first quantitative determinations of whole blood iron were made by Le Canu, Prevost and Dumas³ in 1820 Andral and Gavarret⁴ followed with some observations in 1842, as did Bequerel and Rodier⁵ in 1845, and C A Schmidt⁶ in 1850 Subsequently, several other observations were made, notable among which were those obtained by means of Jolles' ferrometer Although the figures obtained by Le Canu and his co-workers and by Andral and Gavarret are not available,

TABLE 1—*Observations of Early Workers on the Iron Content of Whole Blood of Normal Persons*

Author	Year of Observation	Iron Content, Mg per 100 Cc
Bequerel and Rodier, quoted by Fowell Quart J Med 6 179, 1912 1913	1845	0 0555 male 0 051 female
Schmidt, C A Ibid	1850	0 0512 male 0 0485 female
Pelouze Ibid	1865	0 0506 male 0 0537 female
Jarisch Ibid	1879	0 0506
Biernacki, E Ztschr f klin Med 24 460, 1894	1894	0 0519 male 0 0566 female
Erhen, F Ztschr f klin Med 40 266, 1900	1900	0 0545
Newman, A Ztschr f physiol Chem 37 115, 1902	1902	0 0519
Mayer, A Ztschr f klin Med 40 475, 1903	1903	0 0515
Jolles Deutsche med Wehnschr 24 104, 1898*		0 0486
Hladik, J Wien klin Wehnschr 1 74, 1898* (average of 30 cases)		0 0425
Rosen, H, and Jellinek, S Ztschr f klin Med 39 109, 1900* (average of 10 cases)		0 0527
Jolles and Winkler Arch f exper Path u Pharmacol 44 464, 1900*		0 0575

* These authors obtained their values by means of the Jolles ferrometer

those of other of the early workers are given in table 1 in percentage by weight of whole blood

In 1918, Berman⁷ recorded the blood iron in six instances with an average of 48 6 mg per hundred cubic centimeters of blood, but

3 Le Canu, Prevost, and Dumas, quoted by Biernacki, E Ztschr f klin Med 24 460, 1894

4 Andral and Gavarret, quoted by Meyer and Gottlieb Pharmacology, Clinical and Experimental, trans by John T Halsey, Philadelphia, J B Lippincott Company, 1914

5 Bequerel and Rodier, quoted by Fowell, P H C Quart J Med 6 179, 1912

6 Schmidt, C A, quoted by Fowell (footnote 5)

7 Berman, L A Rapid Method for the Determination of Iron in Small Quantities of Blood, J Biol Chem 35 231, 1918

did not state whether or not human blood was used. In 1922, Brown⁸ stated that the figure for normal blood iron varies between 45 and 52 mg per hundred cubic centimeters, but did not state the source of his figures. In 1926, Mengert-Presser⁹ quoted van den Beigh and Engelkes as having stated that the normal figure for blood iron is 45 mg per hundred cubic centimeters of blood.

In table 2 are recorded figures representing the iron content of the whole blood. Twenty-one determinations were made on the blood of

TABLE 2—*Observations of the Whole Blood Iron, Red Blood Cell Count, Iron Index, Cell Volume and Hemoglobin on the Blood of Eighteen Normal Young Men*

	Iron, Mg per 100 Cc	Red Blood Cells, Millions per C mm	Iron Index	Hematocrit Total Cell Volume	Individual Cell Volume ×10 ⁻¹¹ Cc	Hemoglobin, Gm per 100 Cc
M-1	50 00	5 77	8 7	43 40	8 5	15 73
M-2	47 60	5 98	7 9			15 58
M-3	46 86	5 53	8 5	43 60	8 8	15 73
M-4	46 80	5 17	9 1	45 60	8 8	15 73
M-5	46 00	5 31	8 7	45 60	8 6	15 32
M-6	45 70	5 72	8 0			17 10
M-7	45 60	5 44	8 4			14 70
M-8	45 60	5 32	8 6	43 60	8 2	14 90
M-9	45 60	5 21	8 8	41 70	8 0	15 40
M-10	45 20	5 55	8 2			14 52
M-11	44 80	5 47	8 3			15 90
M-12	44 50	5 36	8 3			14 52
M-13	44 40	5 63	7 9			14 58
M-7 A	44 12	5 19	8 5	43 54	8 4	13 52
M-14	43 80	4 87	9 0	42 09	8 6	15 20
M-15	43 50	5 47	8 0	40 00	7 3	14 77
M-16	43 40	4 78	9 0			13 84
M-14 A	43 20	5 32	8 1			14 88
M-17	42 60	5 34	8 0	45 90	8 6	13 80
M-16 A	42 40	4 84	8 6			15 40
M-18	42 00	5 04	8 4			14 88
Average	44 84	5 35	8 4	44 50	8 38	15 06

eighteen normal young men, the ages ranging between 20 and 40 years. It may be seen in this figure that the red blood cell counts vary between 4,780,000 and 5,980,000 cells per cubic millimeter, the average being 5,350,000. The hemoglobin varied from 13.52 to 17.1 Gm, the average being 15.06 Gm per hundred cubic centimeters of blood. The iron content of the whole blood varied from 42 to 50 mg of iron per hundred cubic centimeters of blood, the average being 44.84 mg. The iron index calculated from the red blood cell count and the iron content of the blood varied from 7.9 to 9.1, the average being 8.4.

⁸ Brown, A. L. A New Quantitative Method for the Determination of Iron in the Blood, *J. Am. Chem. Soc.* **44**, 423, 1922.

⁹ Mengert-Presser, H. Bestimmungen von Hamoglobin und Eisen im Blut unter tropischen Verhältnissen, *Mededeel. v. d. dienst d. volksgezondh. in Nederl.-Indië* **3**, 240, 1926.

In ten instances the individual cell volume was determined from the red blood cell count and the total cell volume calculated from the hematocrit as previously described by one of us¹⁰ This figure varied from 73×10^{-11} to 88×10^{-11} cc, the average being 838×10^{-11} cc

In table 3 are recorded similar observations made on the blood of twenty-one normal young women also ranging in age between 20 and 40 years In this group the red blood cell count varied from 4,440,000 to 5,470,000 cells per cubic millimeter of blood, the average being 4,920,000

TABLE 3—*Observations of the Whole Blood Iron, Red Blood Cell Count, Iron Index, Cell Volume and Hemoglobin on the Blood of Twenty-One Normal Young Women*

	Iron, Mg per 100 Cc	Red Blood Cells, Millions per C mm	Iron Index	Hematocrit Total Cell Volume	Individual Cell Volume $\times 10^{-11}$ Cc	Hemoglobin, Gm per 100 Cc
F-1	46.86	5.14	9.1			13.80
F-2	46.40	5.11	9.0	43.6	9.1	14.63
F-3	45.45	5.47	8.3	47.7	8.8	14.63
F-4	44.80	4.72	9.5	42.6	9.0	14.21
F-5	43.60	4.90	8.7	41.8	8.3	14.63
F-6	41.20	5.35	8.1			15.20
F-7	42.76	4.84	8.8	37.9	7.8	14.00
F-8	42.33	5.21	8.1			13.25
F-9	42.24	4.57	9.2	40.3	8.8	14.21
F-10	41.80	4.83	8.7			14.70
F-11	46.40	4.91	8.5			13.66
F-12	41.60	5.08	8.2	39.7	7.8	13.50
F-13	41.20	4.57	9.0	40.2	8.8	13.66
F-14	40.55	4.91	8.3	41.7	8.5	13.25
F-15	40.55	4.80	8.5	37.3	7.8	13.25
F-16	40.50	4.44	9.1	37.4	8.4	12.56
F-17	40.00	4.63	8.7			15.40
F-18	39.99	4.64	8.6	41.9	9.0	13.52
F-19	39.45	5.00	7.9	45.2	9.0	13.25
F-20	39.33	5.20	7.6	41.8	8.1	13.39
F-21	38.80	4.96	7.8	39.6	8.0	13.25
Average	42.48	4.92	8.6	41.2	8.4	13.90

The hemoglobin varied from 12.56 to 15.4 Gm per hundred cubic centimeters of blood, the average being 13.9 Gm The iron content of the whole blood varied from 38.8 to 46.86 mg per hundred cubic centimeters of blood, the average being 42.48 The iron index calculated as previously discussed varies from 7.6 to 9.5, the average being 8.6

In this group of subjects, determinations of the individual cell volume were made as previously described in fifteen instances This figure varied from 78×10^{-11} to 91×10^{-11} cc, the average being 84×10^{-11} cc

A comparison of the tables for males and females shows that the range and the average figure in each column is slightly higher in males

10 Murphy, W. P., and Fitzhugh, G. Blood Cell Size in Anemia Its Value in Differential Diagnosis, *Arch Int Med* 46:440 (Sept.) 1930

than in females, with the exception of the iron index in which the range is greater and the average slightly higher in the females

Observations were made of the iron content of the blood in twenty-one persons in whom the hemoglobin level and red blood cell count were considered to be essentially normal in spite of the presence of some variation from normal in the state of health. Ten of this group had diabetes mellitus. The patients were of both sexes and of widely varying ages. In this group the hemoglobin varied between 11 and

TABLE 4—*Observations of the Whole Blood Iron, Red Blood Cell Count, Hemoglobin and Iron Index on the Blood of Twenty-One Persons with No Fundamental Disturbance of the Blood*

	Iron, Mg per 100 Cc	Red Blood Cells, Millions per C mm	Hemoglobin, Gm per 100 Cc	Iron Index	Diagnosis
M-1	53.10	5.55	12.62	9.5	Migraine
F-2	50.20	6.53	16.32	7.7	Diabetes mellitus
F-3	44.00	5.60	13.21	7.9	Diabetes mellitus
F-4	43.20	5.41	15.10	8.0	No disease
F-5	43.20	4.95	14.35	8.7	Asthmatic bronchitis
M-6	43.20	4.62	16.32	9.3	Jaundice (infectious)
M-7	42.24	4.57	14.20	9.2	No disease
F-8	42.50	4.69	11.00	9.1	Diabetes mellitus
F-9	41.60	4.90	14.60	8.5	Chronic infectious arthritis
F-10	41.20	4.75	14.45	8.7	? Epilepsy
M-11	41.00	4.66		8.8	Diabetes mellitus
F-12	41.00	4.63	12.70	8.8	No disease
F-13	40.96	4.75	12.90	8.6	Diabetes mellitus
M-14	40.53	4.59	13.76	8.3	Agranulocytosis
F-15	40.40	5.37	12.62	7.5	Diabetes mellitus
F-16	40.40	5.07	12.90	7.9	Diabetes mellitus
F-17	40.20	4.83	16.20	8.3	Obesity
M-18	40.00	4.85	13.76	8.2	Diabetes mellitus
M-14A	39.99	4.68	13.40	8.5	Agranulocytosis
F-19	38.50	5.91	13.95	6.5	Diabetes with complications
F-20	37.50	4.49	12.42	8.4	No disease
M-21	37.00	4.58	14.60	8.1	? Lead poisoning, acute
	41.90	5.01	13.88	8.4	

16.32 Gm per hundred cubic centimeters of blood, the average being 13.88. The red blood cell counts varied between 4,490,000 and 6,530,000 per cubic millimeter of blood, with an average of 5,010,000. The figure for whole blood iron varied between 37 and 53.1 mg per hundred cubic centimeters of blood, with an average of 41.9. The iron index varied between 6.5 and 9.5, with an average of 8.4.

An average of the figures for whole blood iron obtained in the three normal groups which included sixty-four determinations on the blood of sixty persons gave 43.1 mg per hundred cubic centimeters, with a range from 37 up to 53.1. In only one instance was the figure above 50 and in only eight was it below 40.

That the iron index is a rather constant figure in persons with no essential variation from normal in the blood is evident from an analysis of tables 2, 3 and 4. Of sixty-four determinations of this

figure that were made on the blood of sixty persons, 45, or 70 per cent, fell within the range of from 8 to 9. In nine instances the figure was above 9 and in ten instances below 8. The average iron index for the sixty-four determinations is 8.46.

Pernicious Anemia—In a group of forty-one persons having unquestioned pernicious anemia, sixty-eight determinations of the whole blood iron and iron index were made. The lowest figure recorded for whole blood iron was 77 mg per hundred cubic centimeters of blood in a patient with 690,000 red blood cells per cubic millimeter of blood. In each instance in this group of forty-one persons, the iron index was 10 or above if the red blood cell count was 4,000,000 per cubic millimeter or lower. The highest iron index recorded is 20.6. In five instances the disease was in a state of remission, with red blood cell counts above 4,000,000 per cubic millimeter, following treatment with liver. In three of these cases the iron index was below 10, the actual figures being 8.4, 9.1 and 9.1. In one of the five cases the red blood cell count was 4,100,000 per cubic millimeter, and the iron index was 10.5. In the last case of the five, the red blood cell count was 4,630,000 with an iron index of 11.5, the patient in this case having barely recovered from a relapse when the determination was made.

The cases of three patients which were not included with the cases of pernicious anemia because of definite complications are of interest. All of the three patients were treated with liver with the usual response. One of them who had rather marked combined systemic disease showed a drop in the red blood cell count, and blood was being lost from the gastro-intestinal tract. Roentgenograms of the gastro-intestinal tract showed a possible carcinoma of the stomach. In this case the iron index was 8.5 with a red blood cell count of 3,530,000 per cubic millimeter. The diagnosis was complicated in one instance by rather severe chronic nephritis, which was present when treatment was begun, and in another by myxedema occurring after somewhat over a year of treatment with liver. The iron index varied in the first case from 9.4 to 10.5 on three determinations and in the second from 9.2 to 10 on four determinations. In both cases the red blood cell counts varied at the time of the observations between 2,300,000 and 3,920,000 cells per cubic millimeter.

From these observations on patients with pernicious anemia, one may conclude that the iron index is high during a relapse, but approaches the normal figure during a satisfactory remission maintained by means of treatment with liver or liver extract. In patients with pernicious anemia having complications tending to produce secondary anemia, the iron index is likely to approach the normal level also, rather than to remain high as in an uncomplicated case in relapse.

In eight patients having an absence of free hydrochloric acid in the gastric contents up to two hours following an Ewald test meal, there was difficulty in making a positive diagnosis. Of these eight patients, five had an iron index which fell within the range generally found in pernicious anemia. Two of the five with a high index also showed evidence of loss of blood from the intestinal tract, one of whom had an extensive adenocarcinoma of the stomach. This patient had a definite rise in reticulocytes following the ingestion of liver extract which was started when the red blood cell count was 1,800,000 per cubic millimeter. The other three cases in which the patients had a high iron index were probably early cases of pernicious anemia in which the diagnosis was made more certain by the observation of an increased

TABLE 5—*Figures Showing the Average Normal Values for the Whole Blood Iron in Normal Persons in Pernicious Anemia and in Chronic "Secondary" Anemia*

Diagnosis	Number of Determinations	Average	Low	High
Normal, male	21	84	79	91
Normal, female	21	86	76	95
Normal, both sexes	22	84	65	95
Normal, all cases	64	84.6	65	95
Pernicious anemia	68		100	206
Secondary anemia	100-200		43	90+

iron index. In three of the eight cases the patients showed a normal iron index on two separate determinations. One of these may have been an early case of pernicious anemia, the other two probably were not. All of these patients had red blood cell counts below 4,000,000 cells per cubic millimeter.

Secondary Anemia—A large series of determinations of the whole blood iron and of the iron index were made on the blood of persons having a secondary type of anemia. Such observations showed a low or low normal iron index figure in the chronic chlorotic type and anemias resulting from chronic loss of blood, regardless of the source of bleeding, and usually a low normal figure in anemia resulting from various chronic infections, accompanying certain types of tumors of the brain and accompanying chronic cardiac disease.

Iron index determinations made on the blood of patients shortly following an acute loss of blood show figures greater than the normal ones. The amount of increase in the figure is dependent on the acuteness and the amount of the hemorrhage, it being only slightly increased above the normal if bleeding occurred in the presence of chronic anemia.

Special Cases—In two patients with sprue observed at a time when slight anemia was present, the iron index was in both within the range of the low normal figures

The figure for iron index was determined on the blood of four patients with leukemia. In two instances it was high (16.8 and 10.6). The first patient had chronic lymphatic leukemia, the second aleukemic lymphatic leukemia, and both had a red blood cell count of approximately 1,000,000 cells per cubic millimeter. One of the patients with a normal figure for iron index had acute lymphatic leukemia with 1,620,000 red blood cells per cubic millimeter, whereas the second patient had chronic myeloid leukemia with a normal red blood cell count.

One patient with multiple myeloma and a red blood cell count of 2,950,000 cells per cubic millimeter had a normal iron index (8). Another patient with severe myxedema and with a normal red blood cell count but a moderate reduction in the hemoglobin had an "iron index" of 9.7.

In two patients with polycythemia the iron index figures were low (7.5 and 6.7).

Special mention may also be made of the iron index figure in six patients having anemia which developed either during pregnancy or acutely following delivery. In five of these patients the iron index was normal or low. In one patient in whom a severe anemia was present after delivery and in moderate degree before delivery, the iron index was 10.9 and 9.6 on two determinations made when the red blood cell level was, respectively, 1.43 and 1.9 millions per cubic millimeter. It remains to be seen whether or not this represents a true pernicious anemia developing during pregnancy.

In five patients having Paget's disease with anemia, two with undoubted pernicious anemia had a high iron index, the other three showed a low figure.

SUMMARY

Determinations of the iron content of the whole blood were made on the blood of a group of persons having an essentially normal hemoglobin level and red blood cell count, and the figures are herein recorded. The average iron content of the blood in normal young men is 44.84 mg. per hundred cubic centimeters of blood, in normal young women, 42.48, and in a group of sixty persons of both sexes and of varying age with an essentially normal blood, the average is 42.74.

It is suggested that a figure to be known as the "iron index" be calculated by dividing the figure for whole blood iron by the red blood cell count in millions of cells per cubic millimeter. This figure normally varies between 8 and 9, the average in this series being 8.46.

In pernicious anemia during relapse, the iron index was always found to be above 10, with a tendency to approach normal during a satisfactory remission following treatment with liver

Except in certain unusual circumstances, the iron index was found to be normal or lower than normal in chronic secondary anemia. Only in anemia resulting from acute loss of blood and in certain of the patients with leukemia was the iron index above normal and in the range generally found in pernicious anemia.

It is suggested from the preceding observations that the iron index is of definite value in distinguishing between pernicious anemia and secondary anemia in most instances, and that the constancy of the figure for whole blood iron in persons with normal blood suggests this as a satisfactory means of following the changes which may occur in the blood during treatment for anemia.

311 Beacon Street

PERNICIOUS ANEMIA WITH FATAL TERMINATION DURING A LIVER DIET

REPORT OF THREE CASES

JAMES B CAREY, M D

MINNEAPOLIS

It has been found that liver or liver extract used in the treatment for pernicious anemia has an effect on the blood only, it has no effect on either the achylia or the sclerosis occurring in the posterior and lateral columns of the spinal cord

There is a tendency to interpret the favorable remissions obtained in the condition of the blood in patients with pernicious anemia treated by liver substance as having some enlightening implications concerning the etiology of the disease. It is easy to say, when these remissions are universally obtained, that some deficiency is being supplied to the patient with pernicious anemia and that therefore the condition must be a deficiency disease. One must not forget, however, that pernicious anemia, as now generally known, presents other important pathologic changes than those seen in the blood. The changes in the blood themselves are of a hemolytic character, as can always be demonstrated by the finding of end-products of such hemolysis in the skin, duodenal contents, urine and feces. The red blood cells in pernicious anemia may be subject to more rapid destruction than normal cells, because of some primary abnormality of the bone marrow, in which case the hemolysis is a secondary and consequent factor, rather than a primary one, but the anemia, after all, is of a hemolytic type. As part of the syndrome there is also achlorhydria in all cases, and subacute combined degeneration of the spinal column in many. In order, therefore, to deduce from any method of therapy an etiologic hypothesis, one should not be too dogmatic until some effect is demonstrated on the whole clinical picture, rather than on a single phase of the condition. Isaacs recently showed that "in pernicious anemia some of the symptoms of a relapse may occur even though a complete blood remission is maintained with liver treatment."

Of course, it is recognized that such relatively static structures as the gastric glands or the spinal cord could not be so easily modified as the more labile blood elements, yet a truly specific therapy should

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² Read before the Minnesota Society of Internal Medicine

* From the Medical Division, the Nicollet Clinic

modify or at least check the progress of all changes occurring in the condition under treatment. All that really happens in a patient with pernicious anemia under treatment with liver substance is that a prolonged remission in the condition of the blood is established, which continues only as long as the liver is administered, when and if the hepatic substance is discontinued, the blood relapses. This result was formerly sought by transfusions, injections of whole blood, arsenic and other stimulating agents. The very nature of the last-mentioned agents precluded their continuous use. Liver or liver extract can be used continuously, and thus provides continuous stimulation to the maturation of new cells, or protection against the hemolysis of poorly formed elements of the blood. In either case, a sufficient number of blood cells are kept in the circulation to maintain health and life.

The kidneys, muscles and stomach also contain whatever substance is necessary. In spite of this continued action or protection, however, the achylia persists, the changes in the spinal cord may progress, and the blood elements often fall to a level above which they do not improve and will recede or become fixed in a condition of chronic "toxic" anemia. Thus, patients may die of pernicious anemia even while on liver therapy.

Before the advent of liver in the treatment for pernicious anemia, patients died in any of several ways. They became the victims of some intercurrent infectious accident, just as any patient might. They died slowly or rapidly of a progressive anemia which none of the then known therapeutic procedures could check. They died as the result of the progress of the lesions of the cord to the condition which can be classed as "tabetic," *i. e.*, with paralysis of the extremities, rectum and bladder and with trophic disturbances.

The three cases that I am presenting illustrate these three types of death in patients suffering from pernicious anemia who were taking adequate amounts of liver or liver extract up to the time of death. All of these patients were on the so-called "Minot-Murphy" diet, consisting of 8 ounces (226.7 Gm.) of liver and 8 ounces of lean, red meat, together with milk, butter and green vegetables daily, and in addition took from three to nine ampules of liver extract no. 343 daily. They died just as many patients died before liver therapy was known or used. It may be only fair to state that these are the only deaths which have occurred in my experience since the use of liver, and are probably less than the number of deaths that could have been expected if liver had not been used. The first patient died a so-called tabetic death, due to the progress of sclerosis of the spinal cord to its ultimate and fatal conclusion, with the blood remaining at a relatively high level of hemo-

globin content and red blood count, the second patient died as the result of a slowly progressive anemia, and the third died as the result of a rapidly progressive aplastic form of anemia

REPORT OF CASES

CASE 1—Dr A N R, a dentist, aged 45, living in Minnesota, reported for examination on March 9, 1927, complaining of diarrhea and weakness of the legs. His father was living and well at the age of 70. His mother died of a cerebral hemorrhage at the age of 64. He had three brothers, all living and well.

He had always been in good health, except for an attack of appendicitis in 1913, for which an operation was performed. An acute, ruptured, gangrenous appendix was removed. In November, 1926, while on a hunting trip, he became so weak and exhausted that he had to return home. He was examined at that time and found to be "anemic." He remembered that in March, 1926, he had had a sore tongue for a few days, but attributed it to smoking. Under tonic and rest he improved until February, 1927, when he became weak after another attack of sore tongue. He was examined more thoroughly at that time, and a diagnosis of

TABLE 1—*Blood Counts in Case 1*

	Hemoglobin, per Cent	Red Blood Cells	Color Index	White Blood Cells
4/14/27	60	3,480,000	0.89	
6/ 8/27	80	4,510,000	0.88	4,150
8/18/27	77	4,500,000	0.89	4,400
9/28/27	80	3,720,000	1.0	5,390
11/ 1/27	80	3,800,000		

pernicious anemia was made. Of interest in his past history is the fact that he had always been subject to intermittent and unexplained attacks of diarrhea. His hair became gray at the age of 25, and his skin had always shown splotchy, pigmented areas.

At the time of the original examination (March 9, 1927) he gave clinical evidence of posterolateral sclerosis of the spinal cord, more marked on the left side, and achlorhydria. Examination of the blood revealed hemoglobin, 63 per cent, red blood cells, 2,800,000, and white blood cells, 3,950. Reticulocytes numbered 5.5 per cent, due, no doubt, to the fact that he had been on a liver diet since his previous examination. The Wassermann reaction of the blood was negative. The liver feeding was continued. A record of the examinations of the blood is given in table 1.

He went to California for the winter, where he continued his diet, he also took three vials of liver extract daily, occasionally increasing the amount to six or nine vials when he felt bad. He did not return for examination until June 11, 1928, at which time examination of the blood showed hemoglobin, 40 per cent, red blood cells, 2,010,000, color index, 1.0, and white blood cells, 3,700. I did not hear from him again during the summer and in the fall he went to Florida. His wife reported that while in Florida he became a "crank" about the use of liver extract, taking nine and at times twelve vials daily in addition to including liver and beef steak in his diet almost every day. He began to show definite indications of mental deterioration. He engaged in wild schemes, jeopardized his finances and was headstrong and violent toward his family when they attempted to inter-

fere He again reported for examination on March 13, 1929, demanding immediate transfusion because he did not feel as well as before His hemoglobin content was 76 per cent, the red blood cells numbered 2,990,000 and the white blood cells 5,450, the color index was 1.31

Neurologic examination revealed a marked increase in changes of the spinal cord, he himself realized this, as he had had to use a cane on account of a distinctly tabetic gait Largely on account of his mental condition, he was placed in a hospital and kept under sedatives In a week he became quiet but rather suspicious and fretful He continued the use of liver extract (no 343) six vials daily On March 19, 1929, examination of the blood showed hemoglobin, 68 per cent, and red blood cells, 3,500,000, on March 27, hemoglobin, 69 per cent, and red blood cells, 3,630,000

He was kept on liver extract—usually six vials, but occasionally nine daily—but the changes in the nervous system became progressively worse He was often disoriented and irrational He had various obsessions and often auditory hallucinations He became weaker and was finally bedridden because of inability to use his legs He became incontinent as to urine and feces, and a decubitus ulcer developed over the sacrum Until his death examinations were made only of the hemoglobin content of the blood, these showed 69 per cent on April 3, 1929, 60 per cent on April 7, 56 per cent on April 15 and 50 per cent on April 20 One of his obsessions was that he was not getting enough liver extract He was therefore allowed to keep a few vials on his bedside table and he took some extract in plain water whenever he desired, no accurate record was kept of these extra amounts

He died on April 22, with a terminal temperature due to an infected bladder, decubitus ulcer and bronchopneumonia

Comment—There can be no doubt but that death in this case was due to the changes in the spinal cord which produced the damage to the bladder and the trophic disturbances of the skin, thus allowing the entrance of systemic infection His condition was identical with that seen in many cases in the past, in which the hemoglobin remained at about 50 per cent and the red blood cells at 2,500,000, but in which mental changes supervened and the tabetic changes progressed to death

CASE 2—Mr C P J, aged 72, a retired farmer residing in Iowa, was first seen at the Clinic in October, 1926, complaining of weakness, anorexia and insomnia

His father died of pneumonia at the age of 63, his mother, of senility at 90 Two brothers died of pneumonia

In 1893, he was supposed to have had a bleeding ulcer of the stomach, during which time he became pale and weak He recovered and was well until 1911, when he had a slight stroke with double vision, from which he recovered In 1920, he had pneumonia and in 1924, influenza In June, 1925, he consulted Dr Woodward of Mason City, Iowa, complaining of dyspnea on exertion, edema and pain in the legs

Examination at that time gave negative results, except for the edema and anemia His hemoglobin content was 58 per cent, the red blood cells numbered 1,440,000, and the white blood cells 4,200 He was given injections of arsphenamine, and his condition improved In October, 1925, his hemoglobin content was 70 per cent, the red blood cells were 3,500,000, and the white blood cells 6,000 In January, 1926, he was somewhat worse and was given another course of arsphenamine

mine. He improved again until April, when he became worse. He stated that at that time arsphenamine was of no avail. He was in the hospital for two months, with no improvement. During this time he had severe diarrhea. On his discharge, examination revealed hemoglobin, 38 per cent, and red blood cells, 1,400,000.

When first examined, in October, 1926, he was very weak and was hospitalized immediately. We obtained the additional history of a sore mouth, supposedly due to dental plates, in the spring of 1926, and some paresthesia of the hands and feet during that summer. When first observed, his hemoglobin content was 8 per cent and the red blood cells numbered 570,000. He was very edematous. During his stay of seven weeks in the hospital he was given a transfusion once, and merbaphen was administered to eliminate the edema, he was placed on dilute hydrochloric acid and liver. He received daily from the diet kitchen at least one-half pound of liver,

TABLE 2—*Blood Counts in Case 2 While the Patient Was in the Hospital*

	Hemoglobin, per Cent	Red Blood Cells
11/ 4/26	19	1,230,000
11/10/26	25	1,430,000
11/17/26	31	1,800,000
12/ 4/26	54	2,390,000
12/11/26	57	2,500,000
12/18/26	63	3,850,000

TABL 3—*Blood Counts After Patient's Discharge*

	Hemoglobin, per Cent	Red Blood Cells	Color Index
1/10/27	75	3,710,000	1 0
2/ 9/27	71	2,900,000	1 2
3/25/27	63	2,540,000	1 2
5/13/27	65	2,500,000	1 3
8/15/27	61	2,570,000	1 2
11/ 2/27	47	2,030,000	1 1

prepared in various ways, and six vials of extract no 343 daily. His appetite was good at all times. Repeated examination showed typical symptoms of pernicious anemia: a lemon yellow skin and sclera, atrophic tongue, hemic heart murmur, edema and evidence of moderate posterolateral sclerosis of the spinal cord. Achylia was present. The Wassermann reaction of the blood was negative. On his discharge, Dec 19, 1926, the hemoglobin content was 63 per cent and the red blood cells numbered 3,850,000.

The blood counts made at the hospital, following the transfusion and institution of liver feeding, and after the patient's discharge are given in tables 2 and 3, respectively.

During all this period he felt fairly well, but in November he complained of weakness again, and showed some edema of the ankles. He went to Florida for the winter, felt well, and did not report again until June 2, 1928, when examination revealed hemoglobin, 52 per cent, red blood cells, 2,430,000, and color index, 1.08. He said that he had kept up a maintenance dose of from three to six vials of liver extract daily and that he ate liver and beef as often as he could obtain them. He had been out in the sun constantly, as his appearance indicated. On his return home in the spring his daughter supervised his diet and medication.

For a short period he used a liquid liver extract with which I had had no experience, but when this was discovered he was advised to abandon its use and return to the original extract, which he did.

At this time he was distinctly weaker, although no changes in the spinal cord or general condition were demonstrated. He decided that he would return to his home in Charles City, Iowa, where he thought he would be more comfortable with a daughter, he died there on Feb 19, 1929. No definite or accurate report concerning his death was received except from relatives, who said that he gradually became weaker and died. His daughter had been instructed as to the liver diet and the proper amounts of extract. He had continued these until he became too weak to eat anything. During his entire period under observation he took adequate amounts of either liver or liver extract daily.

Comment—This patient died as the result of slowly progressive anemia. Undoubtedly, the blood elements were reduced to a lower level after the final readings. A possible factor in this case must have been the age of the patient. Probably even a potent stimulant like

TABLE 4—*Subsequent Blood Counts in Case 2*

	Hemoglobin, per Cent	Red Blood Cells	Color Index
8/22/28	55	2,670,000	1.05
10/25/28	43	1,830,000	1.09
11/19/28	44	1,810,000	1.22
12/21/28	46	1,600,000	1.12

liver becomes ineffective in a man aged 74. He had certainly lived out his expectancy. Nevertheless, he died of anemia while on an adequate diet of liver.

CASE 3—Miss E. D. MacL., aged 68, was sent to the clinic for examination on May 29, 1929. She complained of weakness. Her family history was unimportant. She had had pneumonia in 1918 and some trouble with her joints for the past four years. During this period she had also had paresthesia of the hands and feet, with the "glove-sock" distribution. During the past winter she had become weak and been dyspneic on exertion. On April 19 she entered the Fifth Avenue Hospital in New York, under the care of Dr. C. F. Tenney. His report showed negative results on general physical examination, achlorhydria and, on May 4, 1929, a hemoglobin content of 19 per cent, the red blood cells numbered 1,300,000 and the white blood cells 5,200. Dr. Tenney's clinical diagnosis was pernicious anemia. She received transfusions there on May 7, 13 and 22, the record of the blood counts is given in table 5.

She was also given liver extract and dilute hydrochloric acid. Examination at the clinic on May 29, 1929, showed a marked pallor and signs of posterolateral sclerosis of the spinal cord. The blood pressure was 135 systolic and 62 diastolic. The hemoglobin content was 36 per cent, the red blood cells numbered 2,120,000 and the white blood cells 5,000. She was placed in the hospital, given six transfusions and kept on liver extract—from six to nine vials daily. She was also given liver and beef by order from the diet kitchen. A record of a few of her blood counts is given in table 6.

During her stay in the hospital she had frequent attacks of precordial pain, with dyspnea. A clinical diagnosis of severe anemia, with posterolateral sclerosis of the spinal cord and coronary sclerosis was made. She continued to receive the "liver diet" and extract no 343 up to the time of death. For a short period she received twelve vials daily. On July 23, at 11 30 p m, the patient became restless and tossed about in bed. Morphine failed to quiet her, she became dyspneic and died at 1 30 a m.

An autopsy performed by Dr A E Kumpf, of the Department of Pathology, the University of Minnesota, revealed. The heart weighed 400 Gm with moderate hypertrophy of the left ventricular musculature. The valves were normal. There was marked sclerosis and calcification of both coronary arteries. The spleen weighed 225 Gm. The liver weighed 1,575 Gm. The bone marrow from the

TABLE 5—*Blood Counts in Case 3 Before Hospitalization*

	Hemoglobin, per Cent	Red Blood Cells	White Blood Cells
5/ 8/29	32	2,100,000	
5/13/29	24	1,600,000	5,700
5/14/29	43	2,600,000	
5/18/29	41	2,800,000	5,000
5/21/29	47	1,900,000	
5/22/29	30	2,400,000	

TABLE 6—*Blood Counts After Hospitalization*

	Hemoglobin, per Cent	Red Blood Cells	Platelets	Reticulocytes
6/ 8/29	22	1,800,000		
6/11/29	33	2,100,000	150,000	None
6/14/29	36	2,200,000		
6/18/29	20	2,500,000		
6/28/29	32	2,700,000		
7/ 1/29	28	1,850,000		
7/10/29	30	1,750,000		
7/20/29	26	1,600,000		
7/22/29	18	1,115,000		

center of the shaft of the left femur was yellow, except the part adjacent to the bone, which was dark red. Microscopically, the liver showed slight lymphocytic infiltration of the portal canals and some fatty change of the central parts of the lobules. The spleen showed some hyperplasia of the malpighian corpuscles. Both showed an increase of iron pigment with potassium ferrocyanide stain. The bone marrow showed numerous myelocytes and myeloblasts, a few eosinophils, metamyelocytes and some megakaryocytes. There were no normoblasts or megaloblasts. The spinal cord showed sclerosis in the lateral and posterior columns. The pathologic diagnosis was (1) subacute combined degeneration of the spinal cord, (2) pernicious anemia, probably in the aplastic stage, (3) hemosiderosis in the liver and spleen, (4) moderate metaplasia of the bone marrow, (5) coronary sclerosis in cardiac hypertension, and (6) hypertension of the kidneys.

Comment—The complication of coronary sclerosis undoubtedly had something to do with the sudden death in this patient. The observations at autopsy indicated that there was cardiac and renal disease

which undoubtedly would have eventually caused death without the concurrence of the pernicious anemia. In this patient, however, the blood did not react to the stimulation of either transfusions or liver. To meet a possible criticism, it may be mentioned that the extent of the nephritis was not thought to be sufficient to account for any degree of anemia. Neither was the heart decompensated. The liver, for instance, showed only such degenerative changes as should result from the anemia, and there was not a sufficient amount of passive congestion to account for the failure to react to stimulation.

SUMMARY

Three patients with pernicious anemia died while under treatment with adequate¹ amounts of liver or liver extracts. They died just as one might have expected before the advent of liver therapy, although, with the exception of the third patient, possibly not so rapidly. I do not wish to draw any conclusions from these few cases, but certain comments may be made. Liver therapy apparently has no effect on the ultimate outcome in every case of pernicious anemia. It is too soon to begin to be hopeful that liver substances can indefinitely check the progress of the disease. In considering the result of liver therapy with the idea of deducing an etiologic hypothesis, it must not be forgotten that achylia and sclerosis of the spinal cord are integral parts of the syndrome and that these changes are apparently unaffected by liver. In certain cases it is evident that one must expect death as the result of the progression of disease of the spinal cord, in spite of a relatively good condition of the blood. In other cases, the blood-forming organs become incapable of further regenerative effort, perhaps as the result of the age of the patient, or even conceivably in younger patients because of exhaustive overstimulation. Finally, there are patients with an aplastic marrow who cannot become stimulated initially.

¹ By "adequate" is meant an amount, found in other patients so treated, that will keep the blood count and hemoglobin percentage up to reasonable normal levels, usually to obtain an initial response, nine vials have been used daily, and to maintain the level, from three to six vials daily depending on the amount of liver the patients were eating. All the patients observed were maintained on a modified "Murphy-Minot" diet, as described in connection with the first case.

TUBERCULOUS INFECTION

ATTEMPTS TO PREVENT IT BY SUBCUTANEOUS VACCINATION WITH B C G

JOHANNES HEIMBECK

OSLO, NORWAY

The basis of all work on tuberculosis is the knowledge of tuberculous infection, and when the question of combating the disease by means of prophylactic vaccination arises the conditions influencing the infection become of vital importance. An account of tuberculous infection will therefore be given, with the observations on which vaccination is based, followed by a description of subcutaneous vaccination with B C G and its results.

The common conception of tuberculous infection is that it generally occurs during the early years of childhood. The many difficulties that continually arise, however, when an attempt is made to bring actual facts concerning tuberculosis into line with this theory, for instance, the morbidity at the ages between 20 and 30 years, make one doubt the truth of the theory. And the facts on which the theory is based do not seem convincing, they are too few and too specialized to justify such a general hypothesis regarding infection in childhood. For this reason, the question of tuberculous infection was made the subject of further investigation, and the results are published in the present communication.

The work has been proceeding since 1926, and covers the three social classes which constitute practically the whole population of Norway, as of other countries, namely, the country dwellers and the two classes of townfolk, the middle class and the workers. The subjects were of all ages, the investigations being made on a large scale among the ordinary, presumably healthy population. The method of investigation was Pirquet's cutaneous tuberculin test, as well as an ordinary clinical and roentgenologic examination in special cases.

The Pirquet test was chosen for the following reasons. 1. If not an absolutely infallible test of tuberculous infection, it is so reliable that the percentage of error in mass investigations is negligible, e. g., of 50 persons under 21 years of age giving negative Pirquet reactions not one gave a positive Mantoux reaction with 1 mg. of tuberculin. 2. It is the easiest and quickest method for the investigator, and in the way that it was used in this investigation it is the least trying to

the subjects being tested. After personal experience with from 5,000 to 6,000 tests, the following is the method that I now use. The skin of the upper part of the left arm is washed with ether, and 2 transverse stripes of concentrated old tuberculin (equal parts of human and bovine) 2 cm long, are put on, 5 cm apart. Then the epidermis is cut with a lancet through the stripes of tuberculin, and the arm is left uncovered for ten minutes before the clothes are again put on, to allow the tuberculin to dry. It should be noted that a lancet and not a perforator is used. The perforator often causes a mechanical action which can easily be, and undoubtedly often is, mistaken for a tuberculin reaction. It should also be noted that the control incision is omitted. It was found to be unnecessary in the first 3,000 or more investigations.

The reaction is judged after forty-eight hours. If there is an area of 5 mm or more of redness and infiltration along the tuberculin incisions, the reaction is positive and the test finished. If the reaction is less or is entirely absent, the test is repeated and again judged after forty-eight hours. If it is then positive, the two first tests will usually be strengthened and the reaction in the second test will be more vigorous. Some personal experience is necessary, however, in judging the weaker reactions, which are seen especially with increasing age. In most cases, however, the positive reaction is so marked particularly in children, that there is no doubt about it. In children less than 15 years of age the reaction at the first test is so reliable that a second one is unnecessary in mass investigations, as only 0.8 per cent of the children giving a negative reaction at the first test give a positive one at the second (878 cases).

These technical details have been described minutely because the value of an investigation depends on the accuracy of the technic. I shall now pass on to the investigations and their results.

RESULTS OF INVESTIGATION

For purposes of presentation it is easiest to begin with the two classes of town dwellers. These investigations were carried out in Oslo, the capital of Norway, a seaport and industrial town of about a quarter of a million inhabitants. Altogether 3,743 persons—2,188 of the working class and 1,555 of the middle class—were examined. They were arranged in three year groups, the first group from birth to 3 years of age, the second group from 4 to 6 years, and so on, until the age of 30, then in ten year groups up to the age of 50, and, finally, all above this age in one group. The results are shown in figure 1, which gives the percentage of those giving positive Piquet reactions in each group.

In persons of the working class the following results were obtained. Ten per cent of the first group gave a positive reaction, that is, were

infected with tuberculosis, as were 22 per cent of the second group from 4 to 6 years of age, and 23 per cent of the next group, up to 9 years of age, then there began a more rapid increase in the number of infected persons to 38 per cent in the following three year period, reaching 50 per cent in the next group, from 22 to 24 years, there was a steady rise to 85 per cent, and from 28 and 30 years to 98 per cent, while from 40 to 50 years of age all subjects, or 100 per cent, were infected. Thus even among the working class, most of whom lived crowded together in large tenement houses, only the minority were infected with tuberculosis in childhood.

The infection occurred even later in the middle class. Here only 7 per cent of the children up to 3 years of age were infected, and

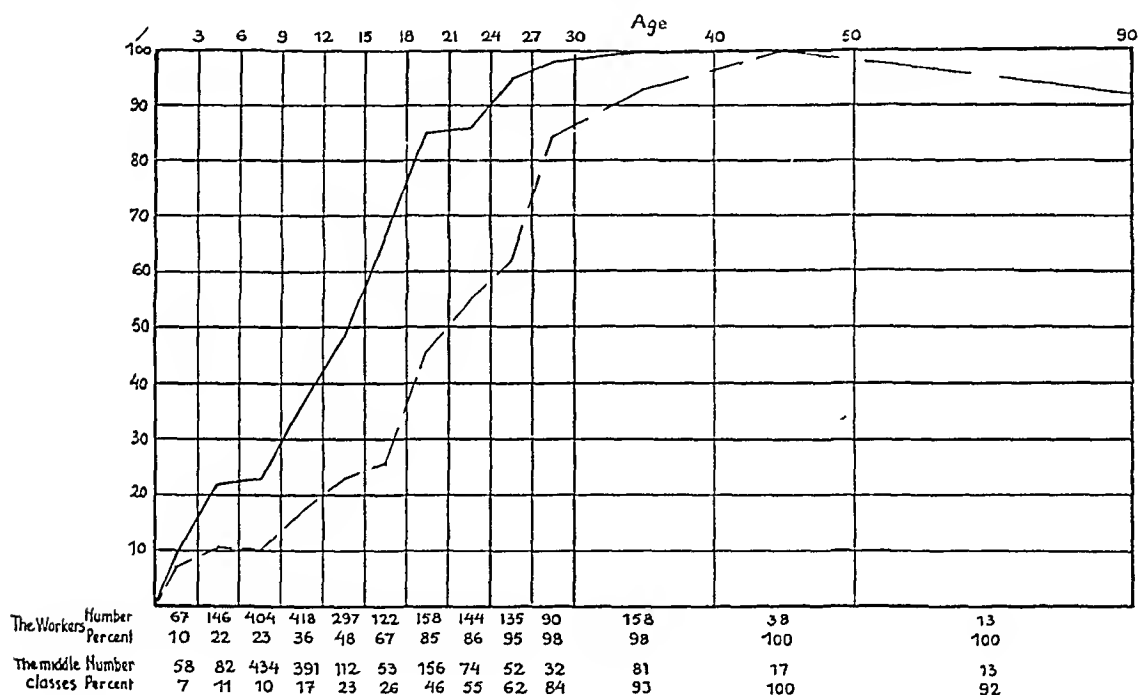


Fig 1—Percentage of tuberculous infection among working class (solid line) (2,188 persons examined) and middle class (broken line) (1,555 persons examined)

the percentage rose slowly during the subsequent age periods until the age of 18, when 26 per cent were found to give positive reactions. After this age, however, there was a sharp rise, so that the number of infected persons reached 84 per cent in the course of the following 12 years, then the rise continued more slowly until the age of 40 to 50 years when every person examined was infected.

From these Pirquet curves one can draw the following conclusion which is particularly well brought out by the curve for the middle class. In childhood only a small number are infected with tuberculosis and the percentage increases slowly during this period of life, as the children, as a rule, are kept at home. When they are infected at this age it is

usually because there are cases of tuberculosis in the home. Therefore the first period of infection is usually in the home during childhood. Then, with the transition to a working life with its unlimited intercourse with other people and the many chances of infection outside the home, the second and great period of infection begins. It is in this period of youth, the working years, that the majority of people, and all who have escaped the infection during childhood, become infected. Owing to the different social conditions, this period starts earlier and is less marked in the working class than in the middle class.

The fact that a small number of persons are infected during childhood and the majority later in life is naturally also met with among

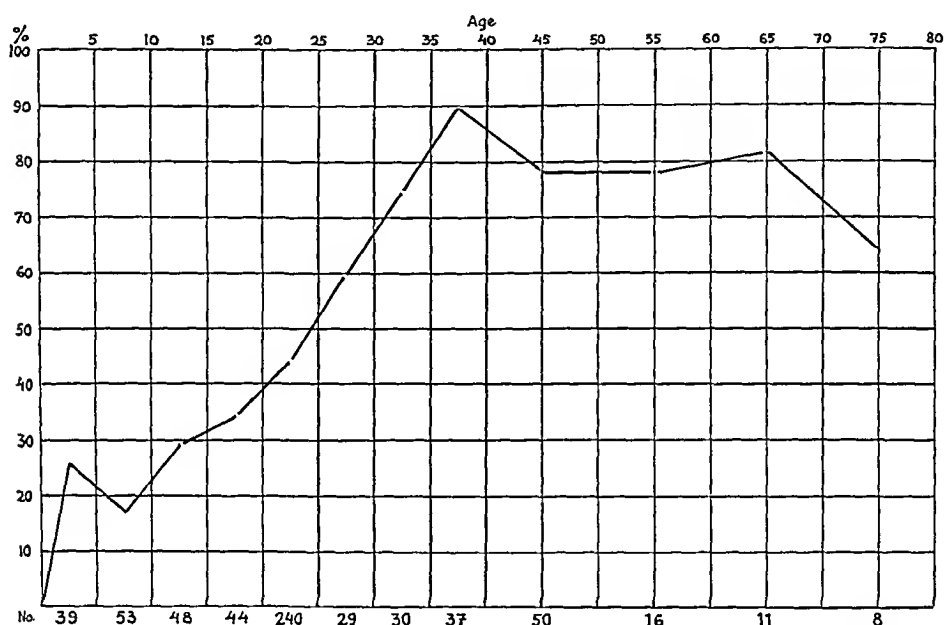


Fig 2—Percentage of tuberculous infection among persons in country districts. Scale at bottom of chart gives number of persons examined.

the unmixed country population, as is evident from figure 2, which shows the results by five year age groups. But among these people, whose life passes uneventfully and in the same surroundings from cradle to grave, the curve of infection runs smoothly, and by no means all persons become infected.

The foregoing conclusions can be drawn from ordinary investigations with the Pirquet reaction. I shall now consider how far they are confirmed by more specialized investigations.

I shall first deal with infection during childhood, in which a marked difference between the two town classes was shown by an investigation of school children. This is indicated in figure 3, which shows the results of the Pirquet test (a) in the school in Oslo which contains pupils

from the most typical and poorest working class district of the town, and (b) in the school composed of children from the most prosperous class of the town. The percentage is given for each year class and it will be noticed that it rises slowly for both groups, although more rapidly for children of the working class than for those of the middle class, also that the infection is twice as common among the former children as among the latter.

The relationship between the curves indicating infection and those indicating morbidity for Oslo is shown in figure 4. The newly recorded cases of tuberculosis for one year are arranged in five year age groups.

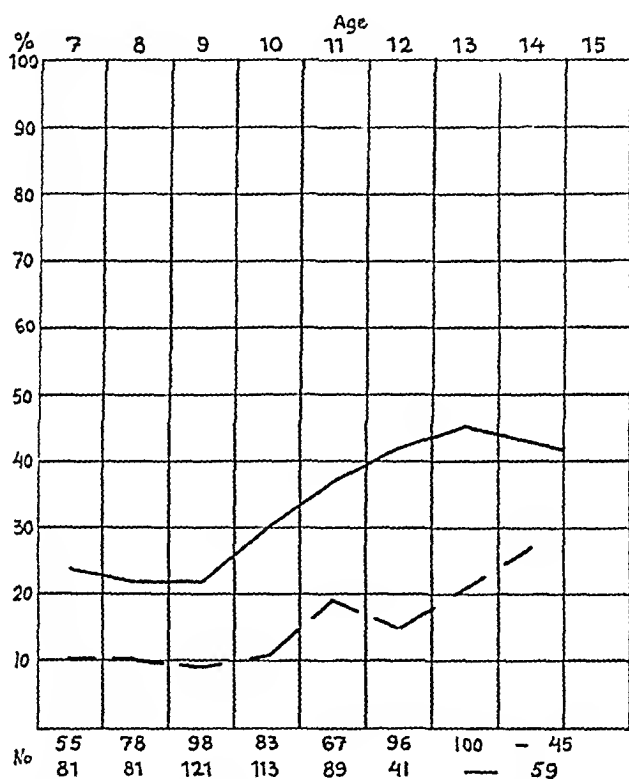


Fig 3—Percentage of tuberculous infection among school children of the working class (solid line) and of the middle class (broken line). Figures below chart indicate the number of children of the working class (upper row) and middle class (lower row) examined.

and are placed in columns. The morbidity was slight during the few cases of infection during childhood, whereas it was widespread during the young adult period, corresponding to the time when the second—the great—period of infection occurred. Then the number of new cases gradually fell again to zero. The morbidity curve, therefore, confirms the suggested theory of infection and seems to support the view that tuberculous disease is a direct result of the primary tuberculous infection. This question and the significance of the positive and negative Pirquet reactions will be dealt with more fully in the following account of the investigations of tuberculosis among the nurses in Ullevål hospital.

TUBERCULOUS INFECTION IN NURSES

Ullevål hospital is the municipal hospital containing about 1,500 beds, of which approximately 300 are for tuberculous cases. The latter are chiefly advanced cases of pulmonary tuberculosis in the special tuberculous wards in the 3 medical departments, they include also, for various reasons, cases in the other departments of the hospital. It is therefore easy to understand that there is ample opportunity for the nurses to become infected. These nurses are principally probationers in the nursing school of the hospital, the course of which lasts three years, it admits about 110 new probationers every year. All the nurses reside in the hospital and therefore live under similar conditions. These conditions are ideal for the exact study of tuberculous infection with, on the one hand, uniform material consisting of healthy persons of the same age—nurses in training—and, on the other hand, a constant and plentiful supply of sources of infection, with a period of three years for most careful observation.

The investigations were begun in 1924 on the initiative of my former chief, Dr. Olaf Scheel. The plan at first was to obtain Pirquet reactions from the newly admitted probationers and to keep them under observation. By degrees however, the results made it necessary to extend the work to include the aforementioned investigations and other points.

The observations on each group are recorded separately (fig. 4) for 1924, 1925, 1926 etc. The results for the first three years are given in two columns: one for persons giving positive reactions to the Pirquet test and the other for those giving a negative reaction, for the present I am concerned with these only.

The first result, which at the time seemed curious, was that only one half of these women, 21 years of age, two thirds of whom came from the towns and one third from the country, gave a positive Pirquet reaction, that is, were infected with tubercle bacilli, a fact confirmed year after year. This has now been accounted for by the investigations referred to.

The second result which gradually became apparent from observation of the nurses was the overwhelming morbidity of tuberculosis among those who first gave a negative Pirquet reaction and the slight morbidity among those who had a positive Pirquet reaction to start with. This is shown in the columns of figure 5, in which each transverse stroke indicates a case of tuberculous disease. Among the probationers of 1924, 17 of the 51 who started with a negative Pirquet reaction eventually contracted the disease, while there was only 1 case among the 58 starting with a positive reaction. In the class of 1925, there were 21 cases among the 72 giving a negative reaction and 1 case among the 42 giving a positive reaction, in the class of 1926, 15 cases occurred among the 62 with an initial negative reaction and 1 case among the 52 with a positive reaction.

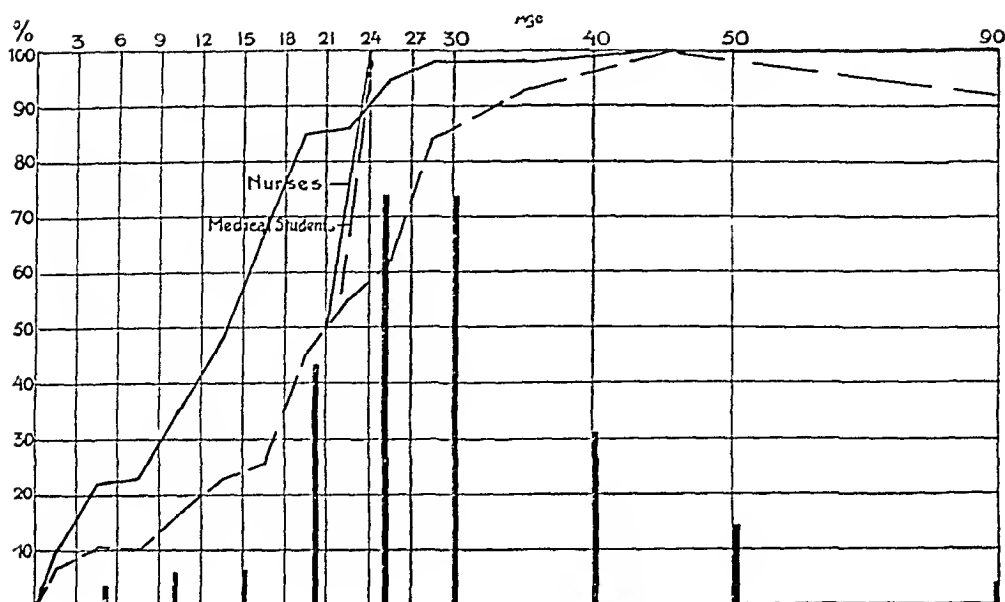


Fig 4—Relation between infection and morbidity curves. Solid line represents working class, broken line, middle class (infection curves for medical students and nurses are indicated), columns, newly reported cases of tuberculosis for one year, arranged in five year age groups

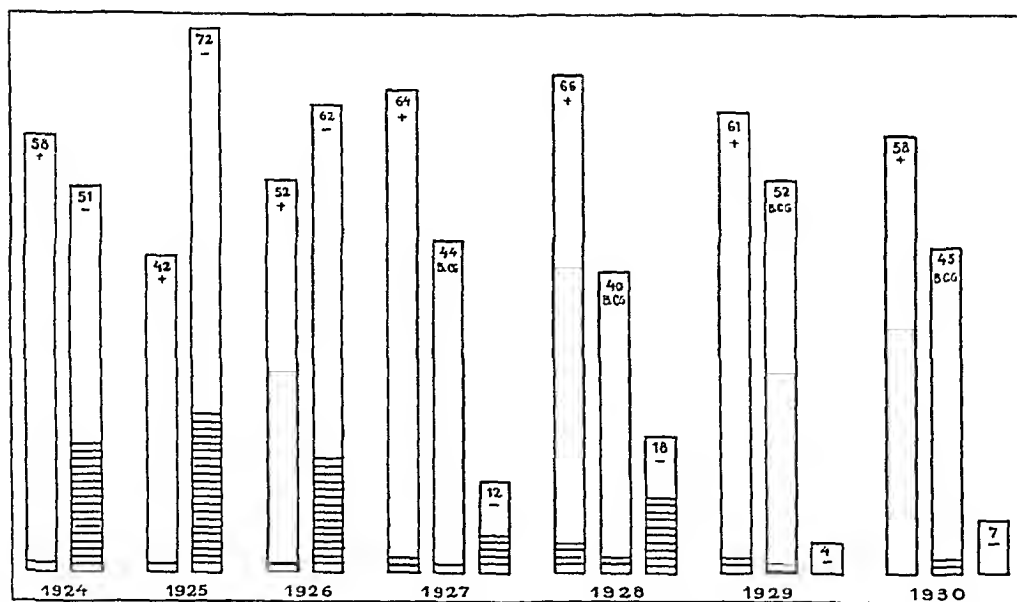


Fig 5—Tuberculous diseases among nurses. The columns marked with a positive sign indicate the group giving a positive reaction at the initial examination, the columns marked with a negative sign, the group originally giving a negative reaction. The other columns indicate the number of persons vaccinated with BCG. The transverse lines in the columns indicate the number of cases of tuberculous disease that developed.

It should be noted that all these nurses were thoroughly examined when they started work at the hospital and were found to be healthy. They had never had any serious illness or presented any symptoms of disease. In this respect they were all alike. They differed from each other, however, as to their Pirquet reaction. Those giving a positive reaction were infected with tubercle bacilli, but as no symptoms of the disease had been or were present the infection must have been benign. The nurses giving a negative reaction were free from tuberculous infection.

The generally accepted opinion that the presence of tuberculosis in persons between 20 and 30 years depends on a latent infection in childhood would lead one to expect that cases of tuberculosis in adults would be found mostly among those who previously gave a positive Pirquet reaction. But this is not so. On the contrary, these persons seldom become ill with the disease. It is among those who, fortunately or unfortunately, have passed through childhood and the first years of youth without contracting a benign tuberculous infection that one finds an appalling morbidity from tuberculosis when they are exposed to infection. How enormous this infection is in the hospital, was further demonstrated by the Pirquet reactions of the nurses during their training, which showed that in the course of their three years' stay at the hospital all, or 100 per cent, become infected. This is shown in figure 4, in which the nurses' curve (unbroken short line) is plotted along with that of the rest of the middle class. The extension of tuberculous infection from 50 to 100 per cent of infected cases, which takes about twenty years in the middle class, under ordinary conditions of infection, occurs among the nurses in the course of only three years, owing to the particularly favorable and abundant chances for infection in the hospital.

That the exogenous bacillary infection, in this case occurring in the hospital, is really the determining factor, is confirmed by investigations carried out on medical students. It was found that 56 per cent of the students gave a positive Pirquet reaction before they began their clinical work at the hospital, but after two years of hospital work there were 98 per cent of positive cases (fig 4, broken short line). This group, the only one exposed to practically the same infection as the nurses were, thus had the same type of infection curve, which was distinct from that of the middle class. Moreover, it showed a remarkably high tuberculosis morbidity, for 19 of the 339 students engaged in clinical work were found to have tuberculous disease.

It is convenient at this point to examine the tuberculous disease among the nurses more in detail, especially because they afford particular information about the relation between tuberculous infection and the disease.

The tuberculous diseases in all the year groups are taken together and specified here

Pulmonary infiltration (21 cases 7 with, and 14 without demonstrated tubercle bacilli)

Erythema nodosum, pulmonary infiltration (16 cases 1 with, and 15 without demonstrated tubercle bacilli)

Erythema nodosum, pleurisy (4 cases)

Erythema nodosum, pleurisy and peritonitis (1 case)

Erythema nodosum (16 cases)

Pleurisy (15 cases)

Pleurisy, pulmonary infiltration (6 cases)

Pleurisy, coxitis (1 case)

Caries of the ribs, pulmonary infiltration (1 case)

There were 81 cases in all, 10 being among the 372 nurses originally giving a positive Pirquet reaction, and 71 being among those first giving a negative reaction

The time when symptoms of tuberculosis were noted in nurses originally giving a negative reaction gives definite information as to the interval of time between infection and the appearance of the disease. During the first six months after training began there were thirty-one cases, during the second six months, sixteen cases, during the whole of the second year, eighteen cases, and after the second year six cases. As one can date the first chance of infection from the day that training started, though no doubt it actually occurred later when the nurses came to work in the tuberculosis wards, it can be concluded that there is not a long latent period between the infection and the outbreak of the disease, but that the infection soon betrays its malignancy. This is clear from the following observations in an individual case

Probationer Randi began her training at the hospital on Jan. 2, 1928. She then had a negative Pirquet reaction. On February 4, a roentgenogram was taken of her lungs, as was done at that time in the case of all the nurses who originally gave a negative Pirquet reaction. As shown in figure 6, it was normal. She did not nurse tuberculous patients during the first six months, and on July 18 she still had a negative Pirquet reaction. In September she started work in one of the tuberculosis departments, and in October she no longer felt well. On October 27, another Pirquet reaction was therefore obtained and a roentgenogram taken. The Pirquet reaction then was a maximum positive one. The roentgenogram (fig. 7) showed that external to the right hilus there was an infiltrated area, about the size of a hen's egg, merging into a diffuse hilar condensation. The next day (October 28), an eruption of erythema nodosum appeared, and she became feverish. A week later, on November 5, the temperature became more irregular with a tendency to rise. On November 8, there was another outbreak of erythema nodosum. A roentgenogram (fig. 8), taken on November 9, showed a distinct enlargement of the previously observed primary infiltration—the German "Fruhm-

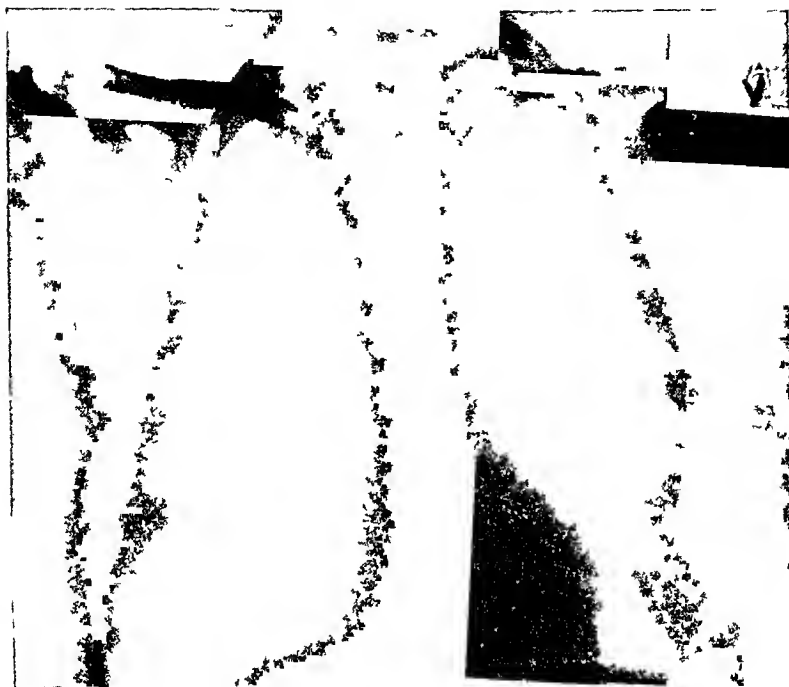


Fig 6—Initial (normal) roentgenogram taken on Feb 4, 1928, in case reported



Fig 7—Roentgenogram taken on October 27

filtrat"—and scattered spots spreading downward over the field of the right lung. Barely two months had elapsed from the date of the probable infection to the onset of the disease.

It only remains to draw conclusions from the fate of the nurses who started with a positive Pirquet reaction. When exposed to the identical infection which caused such a great morbidity from tuberculosis among those who started with a negative reaction, these nurses exhibited a minimum morbidity. As already stated, all that distinguished the two groups from one another was the fact that the group giving a positive Pirquet reaction already had a benign tuberculous infection when



Fig. 8—Roentgenogram taken on November 9

exposed to infection at the hospital. Their resistance against the infection in the hospital can be attributed only to their previous infection, which must have produced immunity against a new tuberculous infection, an immunity here revealed by the Pirquet reaction. This, moreover, is merely a confirmation of Koch and Romei's demonstration of the immunity against reinfection of an animal infected with tuberculosis.

As the Pirquet reaction was therefore, a sign of immunity against a new infection, it at once occurred to me that the natural infection—in which chance decides whether it shall be benign or malignant—might be replaced by an artificial, benign infection which, like the natural one, manifests its immunizing effect in a positive Pirquet reaction. For the production of such an infection it should be possible, theoret-

ically, at any rate, to use B C G, because it differs from the tubercle bacillus only in that it cannot be virulent. Moreover, the use of B C G in cases showing a negative Pirquet reaction would logically conform to Calmette and Guérin's rule for employing it in new-born children threatened with tuberculosis. For, like these, persons giving a negative Pirquet reaction are not infected with tuberculosis, but are extremely susceptible to tuberculosis. The scope of its application has merely been extended from infancy to adult life in conformity with the new theory of tuberculosis expounded here.

However, it would be necessary to modify the method of vaccination, as oral administration in infants is conditional on the permeability of the intestine, which soon disappears. The vaccination must therefore be done by some parenteral route. It was decided to make the injection superficially under the skin. This was done (1) because the cutaneous and subcutaneous tissues are supposed to be the chief sites for the production of antibody, and therefore give the vaccine the best chance of exerting an immunizing effect, and (2) because it was possible to watch the local action of the vaccine and to intervene if necessary.

VACCINATION WITH B C G

On the basis of this reasoning, on the one hand, and with the threat of an enormous morbidity from tuberculosis among the nurses with a negative Pirquet reaction, on the other hand, subcutaneous vaccination with B C G was tried.

It will not be necessary to describe the development of the investigation in detail. I shall mention only the essential points.

The first experiment was carried out in May, 1926, with an arbitrarily chosen dose of 0.2 mg. of B C G, suspended in a physiologic solution of sodium chloride. The result was that barely a month later the Pirquet reaction became positive. As the first step, to produce a sign of immunity, was thus achieved, the investigation was continued. As a cold abscess developed at the site of the injection in both of the first two persons vaccinated, the dose was decreased in subsequent attempts, without, however, dropping below the minimum effective dose. Since then the dose has been reduced to 0.03 and 0.02 mg., but the production of abscesses has not entirely ceased. They have become much rarer, however, appearing in only from 2 to 3 per cent of the persons vaccinated, whereas they occurred in 10 per cent when the large doses were given.

The abscess, which is the only objection to the method, is in every respect a typical cold abscess, and, like the latter, it may persist for a fairly long time. Abscesses of this kind have lasted as long as four months, depending on the treatment and their size. They have never

interfered with the subject's work, however, and have never caused any symptoms except strictly local ones, not even disease of the local glands

I shall now consider the effect of the vaccinations which, after the orienting experiments in 1926, have been carried out systematically since January, 1927, among the nurses at Ullevål Hospital and also among the general population of Norway

In view of the accurate data accumulated concerning infection and the observations referred to, the vaccinations of the nurses have a special interest. Immediately after they started their training and as soon as the Piquet reaction was ascertained, the nurses who wished it were vaccinated. It was done with a suspension of 0.1 mg. of BCG per cubic centimeter, as it was thus easy to measure the dose, the injection was made by the superficial subcutaneous method. After vaccination the nurses were kept away from all patients with tuberculosis for about six weeks, which is the time that usually passes before the Piquet reaction becomes positive, and which is therefore presumed to be the interval that must elapse between vaccination and the development of immunity. To obtain precisely comparable material, the unvaccinated nurses giving a negative Piquet reaction were isolated in the same way. Afterwards they were all free to take up the nursing of tuberculous patients.

Up to the present, 160 nurses have been vaccinated, as shown in figure 5, in which the results for each year are recorded separately. The first year was 1927, when 110 probationers began training, 64 of these gave a positive Piquet reaction—that is, they were immune to tuberculous infection—and 56 gave a negative reaction and were therefore susceptible to tuberculosis. Vaccination was done on 44 of those giving a negative reaction, 12 of the group refusing it. After three years' training, there was only 1 case of illness (pleurisy) among the 44 vaccinated subjects, but 5 of the 12 nurses who refused vaccination had contracted tuberculosis. As in previous years, there was little morbidity among the nurses who originally gave a positive Piquet reaction. The same holds for the year 1928, only 2 of the 40 vaccinated nurses being ill, both with pleurisy, while of the 18 nurses who were not vaccinated some form of tuberculosis developed in 10. The resistance against tuberculosis of those vaccinated with BCG is also evident for the year 1929, as when last observed none of the 52 nurses who were vaccinated in that year had developed tuberculosis, the same applies also to the 24 nurses who were vaccinated in January, 1930. These two periods correspond to the first year and the first six months of training, respectively, periods when, as already pointed out, most of the cases of tuberculosis occur.

The results, then, show that since 1927 there have been 3 cases of tuberculous disease among the 160 vaccinated nurses against 15 among the 35 unvaccinated nurses, and it seems clear that vaccination is effective. This view was corroborated by the Danish statistician, Professor Harald Westergaard, president of the Statistical Commission of the League of Nations, who elaborated the results up to Dec 31 1929. In calculating the morbidity of tuberculosis among the nurses on the basis of the actual, constant number of those in training, he found a morbidity of 4.08 per cent among those with a positive Piquet reaction, of 33.55 per cent among those with a negative reaction and of 2.49 per cent among the vaccinated nurses. Finding that the probable mean error was only one seventh of the actual difference between the two last named groups, he declared it highly probable that the vaccination causes an effective immunity against tuberculosis.

This is also supported by the 2,000 to 3,000 vaccinations carried out simultaneously partly in Oslo and partly in different country districts in Norway. The conditions influencing infection and control are so uncertain, however, that the results are not trustworthy after such a short time, and they will therefore, not be discussed further here.

I have dealt with the chief factor in vaccination with B C G—namely its immunizing action. Other observations made during the experiments are of less importance. A few of them, however, have some interest, both practical and theoretical, and will therefore be referred to.

First, there is the local effect of the injection of vaccine. In most cases there is none, either immediate or delayed, but for a few days after the vaccination a slight redness may appear at the site of the injection, which may be followed by infiltration. Thus infiltration was seen in twenty-seven of the nurses. It may develop at any time from the second week to the second month after vaccination, and varies in size from that of a grain to that of a pigeon's egg. It has been observed to last for as long as twelve months. In some cases the infiltrations suppurred, and in four cases the suppuration led to perforation. It is not clear from the material what causes the infiltration and possible abscess formation, for, as already pointed out, although they were more frequent in connection with the large doses of vaccine, they occurred at random following the small doses. Idiosyncrasy seems to play a part. Another point to be noted is the Piquet reaction in the vaccinated persons.

The basis of all these vaccinations was that a subcutaneous injection of B C G called forth the power of reacting to the Piquet test—an indication of immunity—in persons previously free from tuberculosis. This reasoning, however, proved not to be sound, for even with the larger doses and in cases in which the vaccination caused local infiltration the reaction did not always develop. With the smaller doses,

0.02 and 0.03 mg, barely one half of the subjects gave a positive reaction in the first six weeks to two months. But even when the Pirquet reaction did not become positive the vaccination seemed to produce immunity, a point of the greatest importance though antagonistic to the working hypothesis. None of the twenty-seven nurses vaccinated during the first three years—six in 1926, seven in 1928 and fourteen in 1929—who gave a negative reaction in response to the vaccination contracted the disease when exposed to tuberculous infection. It seems that these also must have become immunized. This form of immunity, however, could not have been an absolute immunity protecting against all infection, because when these twenty-seven nurses were subsequently exposed to infection they gave a positive reaction, undoubtedly due to an exogenous tuberculous infection, for in other vaccinated persons outside the hospital, some of whom have been living in surroundings free from tuberculosis since their vaccination, it is not rare to find a continued negative reaction. The effect of the vaccination seems, therefore, to be that the BCG infection tends to produce a moderate immunity before the appearance of allergy, manifested in the positive Pirquet reaction. This immunity is not strong enough, however, to prevent tuberculous infection, but it prevents the infection from becoming malignant and renders it benign, so that it acts like a new dose of vaccine increasing the production of antibody to a point where it gives an allergic reaction. In harmony, perhaps, with the fact that the BCG immunity only mitigates the effect of subsequent infections is the observation that the positive Pirquet reaction of the vaccinated nurses in tuberculous surroundings remained constant, with one exception, throughout the whole period of observation, but was found to become weaker and disappear in from one to three years in surroundings free from tuberculosis.

CONCLUSIONS

Tuberculous infection occurs in the minority of persons during childhood (the first period of infection) and in the majority during adult life (the second period of infection).

Tuberculous diseases are generally the direct result of a newly acquired infection. An infection that does not presently reveal its malignancy with symptoms of disease but merely causes allergy will seldom give rise to disease processes later, on the contrary, it protects the organism against any new exogenous infection. Pirquet's tuberculin reaction in a healthy person is therefore to be regarded as a sign of immunity. Subcutaneous vaccination with BCG is harmless and, as a rule, produces immunity, often associated with allergy. The immunity is equivalent to a benign tuberculous infection, but is probably not per-

manent As within a certain time, perhaps from one to four years after the vaccination, it seems to be strengthened and stabilized by any later tuberculous infection, those vaccinated possibly ought to be infected with tubercle bacilli or revaccinated with B C G the first year or two after vaccination In persons living in tuberculous surroundings and giving a negative Pirquet reaction, subcutaneous vaccination with B C G is the sovereign means of preventing tuberculosis

PRIMARY CARCINOMA OF THE DUODENUM

REPORT OF FOUR CASES, WITH A REVIEW OF THE LITERATURE

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AND

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CHICAGO

The first report of a case of primary carcinoma of the duodenum is found among the writings of Georgius Hamberger¹ as early as 1746. In 1761, the letters of Giovanni Morgagni² brought to light the clinical pathologic report of the second instance, in which the condition was localized in the first portion of the duodenum. This case was said to have been encountered no later than 1733. Almost a century elapsed before additional instances were recorded. It is noteworthy that among the records and memoirs of Richard Bright³ no reference to this condition is found. Following Chomel's⁴ paper in 1852, and that of Caillet⁵ in 1876, many other reports appeared. Additional instances have continued to appear in the literature.

The present report deals with four cases of primary carcinoma of the duodenum that were observed clinically and diagnosed by a careful study of the microscopic specimens. We have also made a review of the literature. It is our purpose in this article not only to report these cases, but to call attention to the need of careful, critical study and analysis of obstructive duodenal lesions.

REPORT OF CASES

CASE 1—*History*—A P, a white man, aged 45, married, was admitted to the Michael Reese Hospital on June 24, 1929, complaining of jaundice, weakness, loss of weight and itching of the skin. About two months previously, he had been informed that his face was yellow. The jaundice had become progressively deeper,

* Submitted for publication, Aug 13, 1930.

From the Medical Service and Stomach Study Group of Michael Reese Hospital and the Medical Service of the Cook County Hospital.

1 Hamberger, G E. De ruptura intestini duodeni, Jena, 1746, Disputationes ad Historiam et Curationes Morborum, Albertus Hallerius, 1757, vol 3, p 507.

2 Morgagni, G B. De sedibus et causis morborum, Naples, 1761.

3 Bright, Richard. Cases and Observations on Diseases of the Pancreas and Duodenum, Tr Med-Chir Soc, London 18 1, 1832, Abdominal Tumors and Intumescence, London, The New Sydenham Society, 1860.

4 Chomel. Cancer du duodenum, Gaz d hôp 10 37 (Jan 24) 1852.

5 Caillet. De quelques cas d'ictère mécanique dus au cancer de la deuxième portion du duodenum, These de Paris, 1876.

and in the past month it had been accompanied by itching. The urine had become dark. Occasionally, a light-colored stool had been passed. During this period, the patient had lost 45 pounds (20.4 Kg) and had become weak. The appetite had remained good. Nausea, vomiting, abdominal distress, constipation and diarrhea had not been noted.

The past history was not significant. The patient said that he had not had a syphilitic infection.

Examination—The patient was well developed, somewhat emaciated and intensely jaundiced. The pupils were unequal, they did not react to light but did react in accommodation. The liver was enlarged, the edge being felt from 4 to 5 cm below the costal margin. It was smooth and firm, the edge was sharp and not tender. An enlarged, tense gallbladder could be felt. The patellar and achilles reflexes were absent.

Urinalysis showed a dark amber urine with a specific gravity of 1.020. The urine was acid, and showed a faint trace of albumin, sugar, 4+, bile, 4+, and a few granular casts. The stool was clay-colored and soft, and it contained no bile, blood or fat.

Examination of the blood showed hemoglobin 65 per cent, red cells, 3,430,000 per cubic millimeter, white cells, 8,300, differential count polymorphonuclears, 78 per cent, small lymphocytes 18 per cent, large lymphocytes, 4 per cent, sugar, 250 Gm per hundred cubic centimeters, nonprotein nitrogen, 29, icteric index, 200, the van den Bergh reaction, direct and indirect, very strong immediate positive.

An Ewald test meal was given. The stomach contents showed free hydrochloric acid, 34, total acidity, 56 lactic acid, 0, no blood. The total amount of stomach contents obtained by the tube was 125 cc.

Examination of the spinal fluid showed color, transparent, yellow, pressure, normal, lymphocytes 12 per cubic millimeter, globulin, 1 plus, Lange colloidal gold curve, 0123320000 Wassermann reaction, 4+.

Roentgen examination (reported by Dr. R. Arens) showed a defective bulbous duodenum. There was a suggestion of a defect in pressure in the duodenal region, but the observations were not positive. The primary roentgenograms showed a large, well defined shadow of the gallbladder.

Course—A low grade afternoon fever was present throughout the patient's stay in the hospital. Two weeks after admission, potassium iodide and mercurial rubs were instituted as a therapeutic test, on the supposition that we might be dealing with a syphilitic cirrhosis. Shortly after this treatment, the stools became dark and contained occult and fresh blood. The patient commenced to vomit coffee-ground material. He complained of dizziness. The jaundice was becoming less intense, and the icteric index (132) was lower than at the time of admission. The gallbladder was less prominent and not as tense. On the evening of July 10, he vomited 16 ounces of coffee-ground material containing a large clot of blood. Examination of the blood showed 1,200,000 erythrocytes per cubic millimeter and 35 per cent hemoglobin. The patient expired ten hours later.

Diagnosis—The final diagnosis was carcinoma of the head of the pancreas with extension to the liver, duodenum and pylorus, erosion of a blood vessel and questionable tabes dorsalis.

Necropsy—Necropsy was performed by Dr. O. Saphir.

Gross Observation—Gross examination showed that the stomach contained a large amount of partly clotted and partly liquid blood. The duodenum showed a grayish, ragged, irregular, annular tumor. The tumor extended throughout the

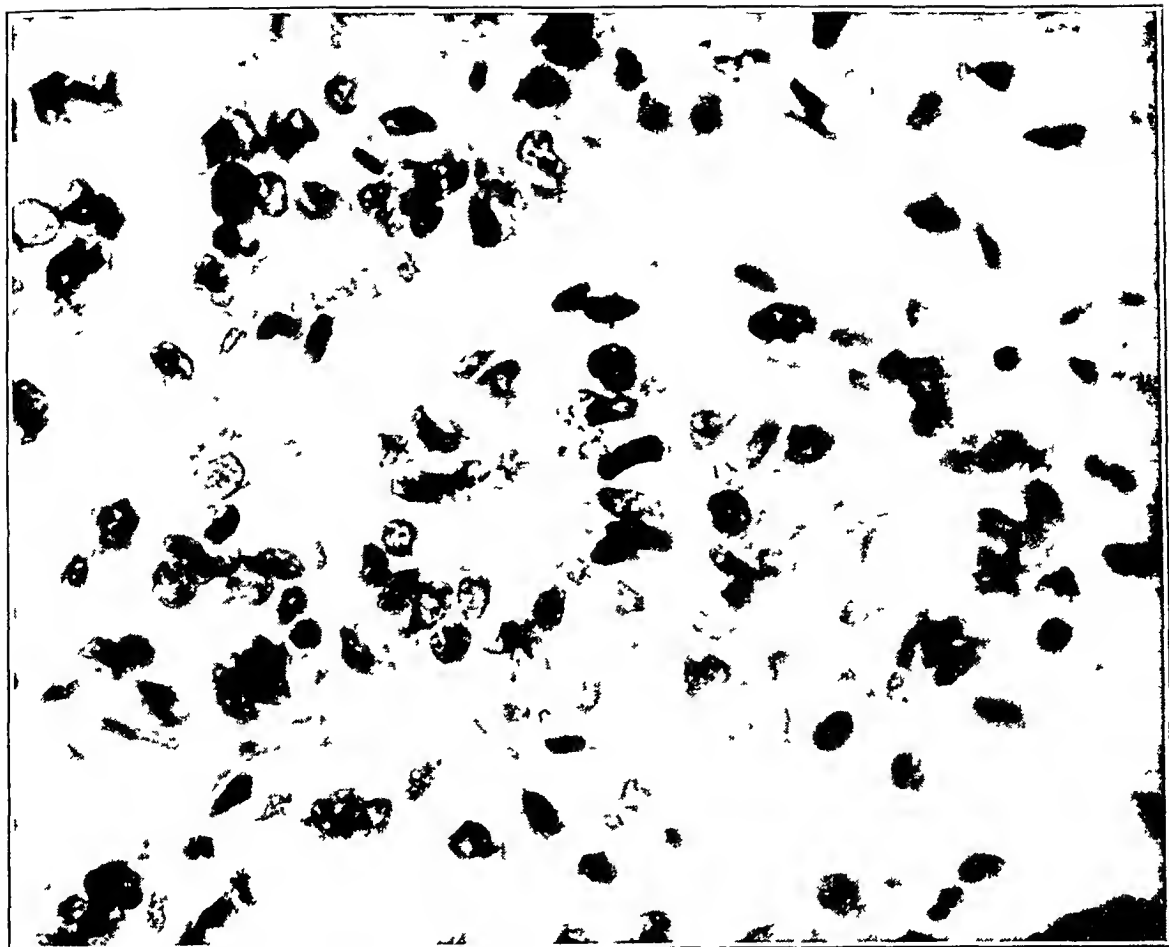


Fig 1 (case 1) —High power magnification showing multinucleated cells and their variation in size and staining quality

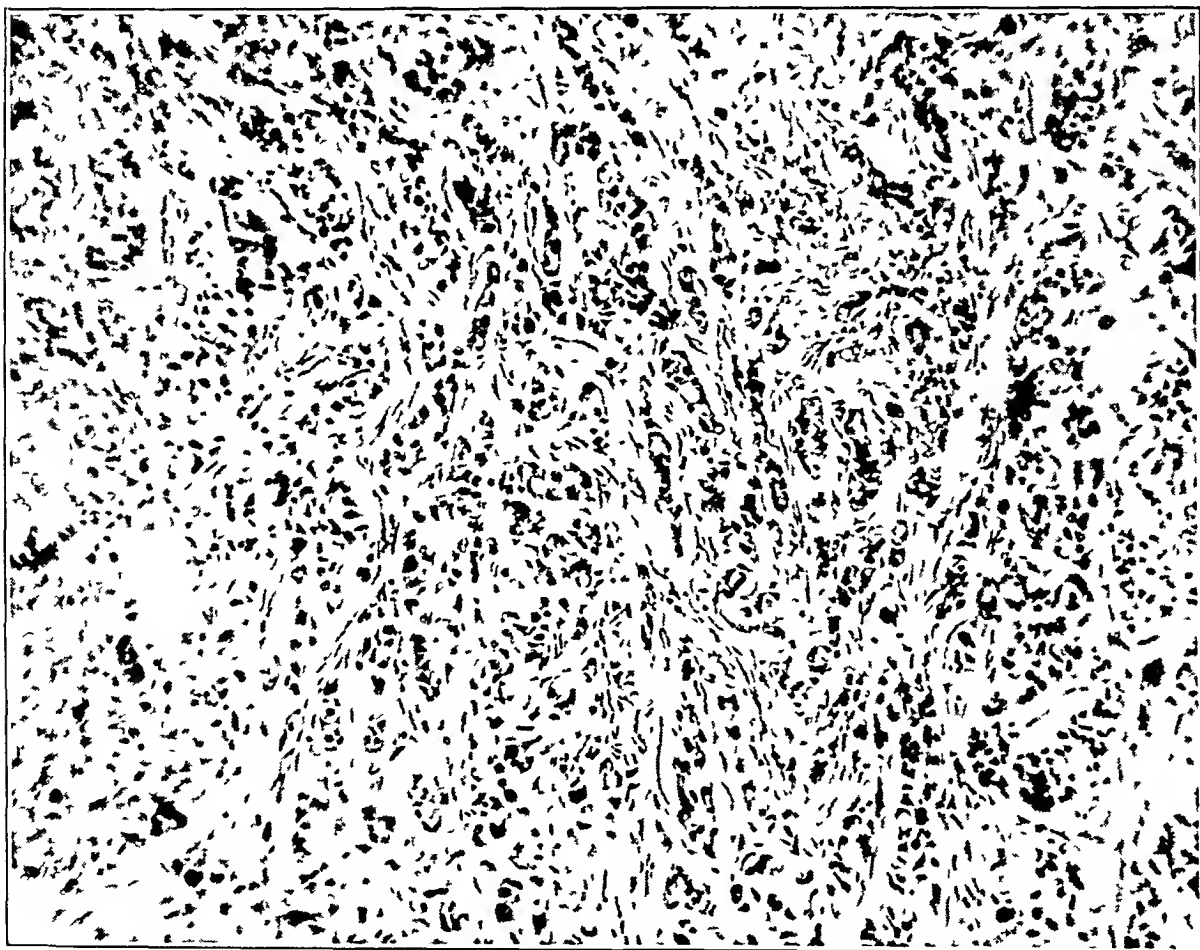


Fig 2 (case 1) —Photomicrograph, showing infiltration of the muscular layer and the new formation of glandular structures

mucosa, submucosa and muscularis and involved the head of the pancreas to some degree. On cut section, it was grayish yellow, but showed a few greenish, more or less circumscribed regions. The common duct opened into the midst of the tumor. The papilla of Vater was completely destroyed. The jejunum and remainder of the gastro-intestinal tract contained a large amount of partly liquid and partly clotted blood. The pancreas was bright yellow, soft and friable. On cut section, hardly any pancreatic tissue could be made out. The pancreatic duct was distended and filled with an almost clear liquid. The liver was enlarged and rather soft and green. There were a few small, circumscribed, yellow and umbilicated nodules throughout the surface. On cut section, they extended into the



Fig 3 (case 1) —Photomicrograph, showing infiltration in the muscular layer and the new formation of glandular structures, as in figure 2

tissue of the liver. On cut section, the liver showed dilated central zones, the bile ducts were distended. The gallbladder was markedly distended, and contained a large amount of almost clear, slightly greenish-tinged bile. The hepatic and common ducts were dilated, measuring as much as 3 cm in diameter.

Microscopic Observations The mucosa and submucosa of the duodenum showed a new formation of glandular structures which were lined by one or two layers of rather high cylindric cells, these cells showed a marked variation in size, shape and staining quality. Mitotic figures were frequent. Some of the cells showed two or three nuclei. An infiltration in the muscular coats was seen in some fields. The parenchyma of the pancreas was almost completely replaced by

a new formation of connective tissue which was richly infiltrated with lymphocytes and endothelial cells. Large numbers of islands of Langerhans were present. The large ducts of the parenchyma were distended.

Diagnosis—The following anatomic diagnosis was made: primary carcinoma of the duodenum (papilla of Vater), with extension to the head of the pancreas and metastases to the liver, hemorrhage of the stomach and intestines, marked dilatation of the gallbladder and of the bile and pancreatic ducts, atrophy of the pancreas, jaundice, secondary anemia, healed endocarditis of the mitral valve and pulmonary emphysema.



Fig. 4—Gross specimen of the duodenum showing the tumor mass in the region of the papilla.

We report this case as one of primary carcinoma of the duodenum, although objections might be raised because of the destruction of the papilla. However, there was no malignant infiltration of the remaining portion of the duct. While it is true that this is possible even though the tumor is primarily of the papilla, the annular mass in the duodenum lends more favor to the view that this condition is a primary duodenal carcinoma. The discussion of the pathology will emphasize the difficulty of differentiating between the two conditions.

CASE 2—*History*—J J, a colored man, aged 36, married, was admitted to the Cook County Hospital on Aug 9, 1929, complaining of pain in the stomach, jaundice, vomiting, clay-colored stools and a loss of 30 pounds (13.6 Kg). Three weeks previously, a severe cutting pain localized in the epigastrium and associated with dizziness and faintness suddenly developed. The intensity of the pain subsided somewhat within a few hours, but remained to the time of examination. Shortly after the onset, the patient vomited, the character of the vomitus being unknown, vomiting had recurred after each meal. Since this acute onset, clay-colored stools, jaundice, itching of the skin, constipation, frequent gaseous eructa-



Fig 5 (case 2)—Gross specimen showing a tumor of the second part of the duodenum

tions and occasionally fullness after eating had been noted. The appetite had become poor, and within a period of three months the patient had lost 30 pounds (13.6 Kg).

Examination—The patient was well developed and well nourished, and did not appear acutely ill. The sclerae were icteric. There was slight tenderness and rigidity in the epigastrium, but no masses were palpable. The blood pressure was 210 systolic and 150 diastolic. The urine contained bile. The Wassermann test gave a negative reaction.

Course—The patient complained of a gnawing sensation in the epigastrium which awakened him at night, it appeared soon after supper and was relieved by belching. A mass was felt in the region of the gallbladder which appeared to be large, rounded and immobile. Roentgenograms of the stomach and the duodenum were normal. Seven days after admission, the patient suddenly passed into coma, the only premonitory symptom being a headache.

Diagnosis—A tentative diagnosis of stones in the common duct, hypertension and cerebral hemorrhage on the left side was made.

Necropsy—Necropsy was performed by Dr. Jaffe.

Gross Observations Gross examination revealed that the abdominal cavity contained about 100 cc of deep yellow, clear fluid, the liver was 6 cm below the xiphoid process and at the costal arch. The second portion of the duodenum was greatly narrowed by a firm, circular mass that measured 4.5 cm in its longitudinal diameter and from 1 to 1.5 cm in thickness. This mass extended downward to about 0.5 cm above the ampulla of Vater. The lumen admitted the middle finger with difficulty. The mucosa was thrown up into firm, light yellowish-pink folds. The first portion of the duodenum was infiltrated by fine pinkish-gray granules. The upper end of the infiltrated area was formed by the pyloric ring. The lowermost part of the second portion showed a diffuse deep greenish-brown discoloration of the mucosa. The liver weighed 1,770 Gm. Its surface was smooth and yellowish brown with distinct dark purplish centers, its consistency was diminished. On the cut surface it was grayish brown, mottled with yellowish brown. There were distinct, fine, yellowish-gray, acinar markings, the intrahepatic bile ducts were markedly dilated and filled with thick green bile. The gallbladder was distended about 11 by 7 cm, the mucosa was deep green and the bile a dark green. The extrahepatic bile ducts were greatly dilated, the common duct admitted one finger easily, the ampulla of Vater was edematous and measured 6 mm in diameter and 8 mm in height. The pancreas was firm, the main duct was diffusely dilated, reaching 12 mm in circumference in the region of the head, the lining was smooth and light grayish white, with a few bright red patches the size of a pinhead.

Microscopic Observations Microscopic examination showed that the tumor was very cellular, the cells being arranged in the form of cords and smaller and larger alveoli. Here and there distinct glandular structures and irregularly shaped tubuli lined by high epithelium were found. The connective tissue septums contained large lipid-filled histiocytes. The type cell was cuboidal or polyhedral. It had a slightly oxyphilic cytoplasm and a large round or oval nucleus, the chromatin of which was arranged in fine granules. There was a small basophilic nucleolus. Mitotic figures were numerous. The liver showed marked dilatation of the intercellular bile capillaries in the central portions of the acini. Thick casts of bile filled the capillaries, and bile droplets were found in the liver cells and the enlarged Kupffer cells. In the periphery of the acini, the liver cells were free from bile pigment and appeared well preserved, with occasional small lipid granules. Much fat was seen in the Kupffer cells. The periportal tissue was infiltrated by lymphocytes and eosinophilic leukocytes.

Diagnosis—The following anatomic diagnosis was made: adenocarcinoma of the second portion of the duodenum with marked narrowing of the lumen, metastases to the peripancreatic, periaortic, mesenteric and left supraclavicular lymph nodes, edema of the papilla of Vater, marked dilatation of intrahepatic and extrahepatic bile ducts and of the pancreatic duct, recent hemorrhage in the pons, perforating into the fourth ventricle, recent encephalomalacia in the left globus pallidus, eccentric hypertrophy of the heart, moderate sclerosis of the coronary

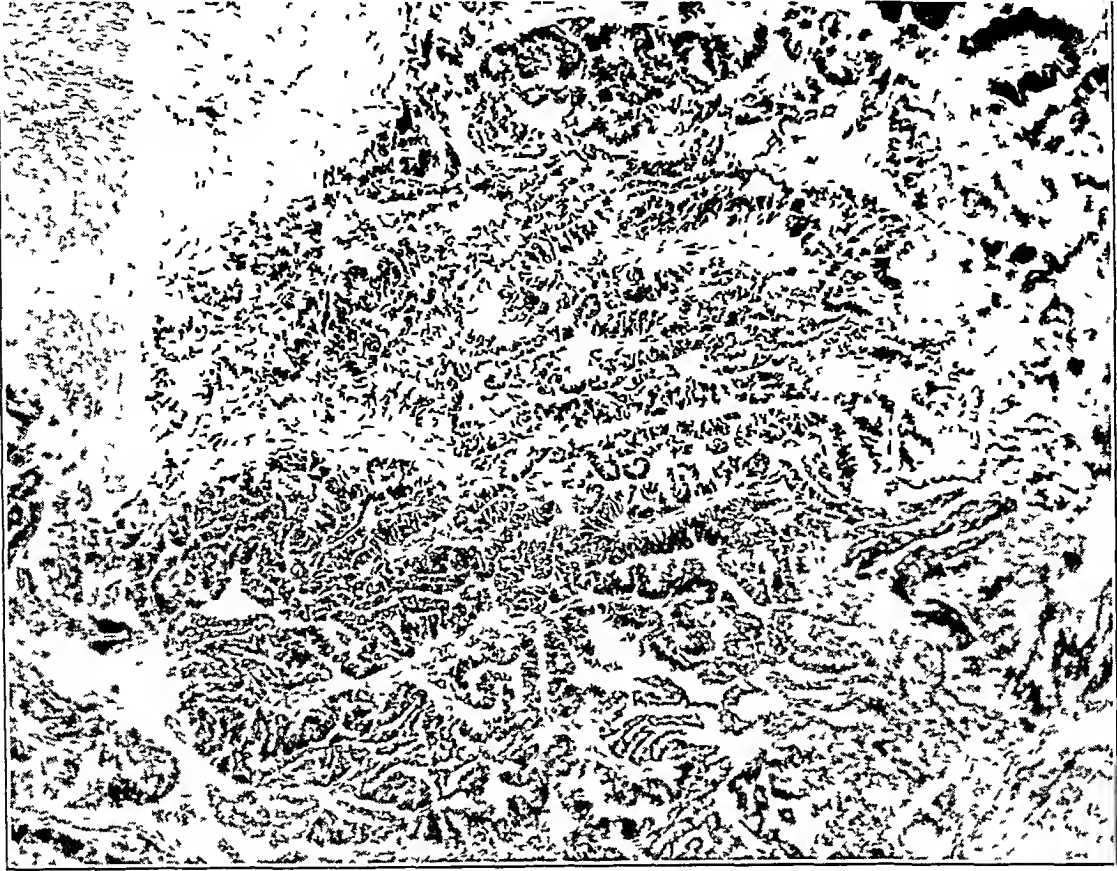


Fig 6—Photomicrograph showing glandular structures and irregular tubuli

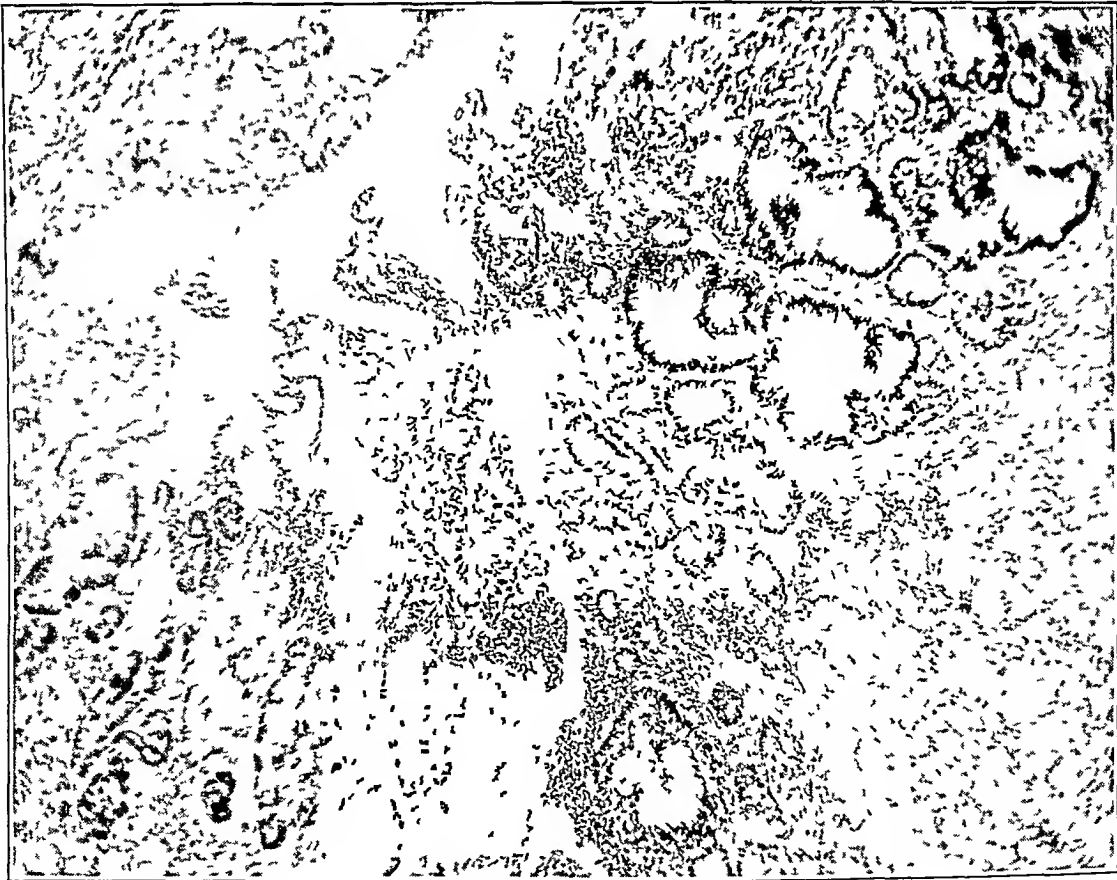


Fig 7—Photomicrograph showing the tumor invading the submucosa

arteries and marked sclerosis of the cerebral arteries, marked icteric discoloration of the sclerae and internal organs, icteric nephrosis and arteriosclerosis of the kidneys, infectious softening of the spleen, hyperemia and edema of the lungs, slight ascites

CASE 3—*History*—J M, a white man, aged 55, married, was admitted to the Cook County Hospital on Feb 10, 1929, complaining of epigastric pain, the loss of 50 pounds (22.7 Kg) and clay-colored stools. The patient considered himself in excellent health until five months before admission, when transitory stabbing pain in the epigastrium had appeared after meals. The pain had recurred until three

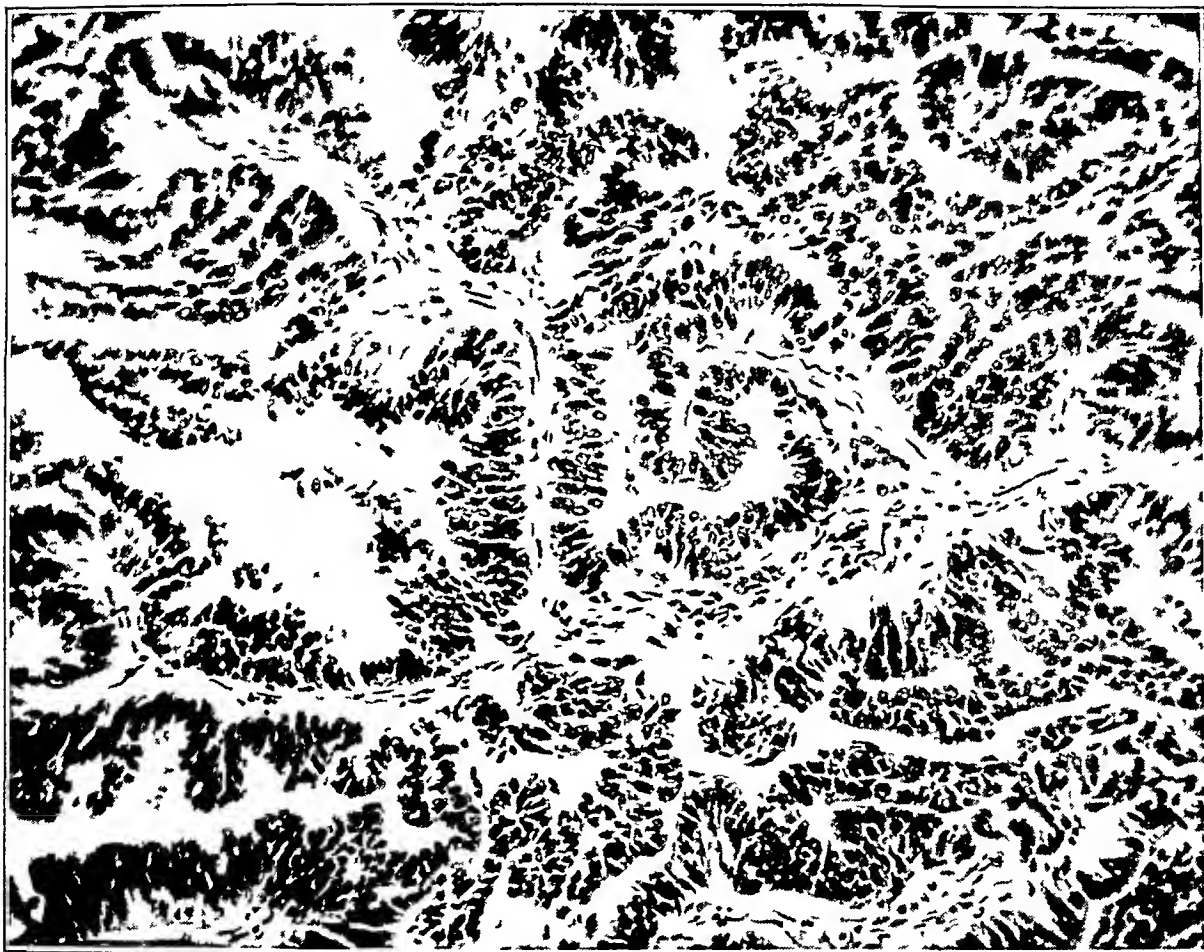


Fig 8—High power magnification of figure 6. Note the presence of several layers of lining cells and mitotic figures.

months previous to admission, when it became more severe, continuous and burning. Food seemed to intensify the pain, and as a result he was afraid to eat. He was unable to sleep because of the intense pain. Gaseous eructations became frequent and bothersome. He was placed on a diet consisting of milk and crackers, and he was given "powders." Though the belching was relieved, the pain was unaffected. Six weeks previous to admission, nausea appeared and persisted to the time of admission. The appetite became poor. Three weeks previously, he had noted the appearance of clay-colored stools. Swelling of the ankles had been present for one week. He had lost 50 pounds (22.7 Kg) in two months and had grown progressively weaker.

The past history revealed that the patient had had influenza in 1919. His wife had had three miscarriages. There were no children.

Examination—The patient was well developed and emaciated, and he appeared quite ill. The skin had a light icteric hue. The sclerae were distinctly icteric. The abdomen was distended, with a tender mass palpable just to the right of the midline below the costal margin of the gallbladder. The edge of the liver was felt 2 cm. below the costal margin and was not tender. The other physical observations were normal. The blood pressure was 102 systolic and 68 diastolic.

The Wassermann reaction of the blood was negative. Examination of the blood showed sugar, 136, urea nitrogen, 17.3, hemoglobin, 35 per cent, red cells, 2,400,000, white cells, 16,200, polymorphonuclears neutrophils, 94 per cent, small lymphocytes, 6 per cent and platelets, normal.

The urine was normal, except for a trace of bile, the stools were dark brown with occult blood. An Ewald test meal was given, after fifty-five minutes, the free hydrochloric acid was 34 and total acidity, 44.

A tentative diagnosis of carcinoma of the stomach with metastases to the liver, carcinoma of the bile ducts and carcinoma of the head of the pancreas was considered.

Course—Roentgenograms of the stomach and duodenum gave normal results. The patient had a low grade fever continuously, the maximum temperature being 100.8 F. in the evening. The jaundice increased. On February 19, the icteric index was 37.5, and the van den Bergh reaction was negative. The patient grew progressively weaker. The anemia increased, and the leukocytes rose to 20,400. On the evening of February 21, he complained of sudden severe pain in the right hypochondrium radiating about the umbilicus, he died about nine hours later. A diagnosis of carcinoma of the pancreas was made.

Autopsy—Necropsy was performed by Dr. Jaffe.

Gross Observations—Examination showed marked emaciation and anemia, and icterus of the skin, sclerae and mucous membranes. The abdomen contained 2,000 cc. of cloudy, light yellow fluid. The stomach was dilated and filled with bile-stained material. In the second portion of the duodenum, just below the papilla of Vater, there was a fungoid, soft, light gray mass, 5 cm. in length and 6.5 cm. in its transverse diameter, involving three fourths of the circumference of the duodenum and protruding about 10 mm. into the lumen. The common duct was greatly dilated being 4 cm. in circumference. The hepatic duct was 6 cm. in circumference at the bifurcation, the cystic duct, 1.5 cm. in circumference, and the pancreatic duct, 7 mm. in circumference. The edge of the liver was 3 cm. below the xiphoid process and 2 cm. below the costal arch. The surface was studded with whitish hyaline plaques and yellowish-gray nodular elevations up to 4 mm. in diameter. The cut surface was deep brown, the intrahepatic bile ducts were dilated, being as much as 6 mm. in diameter. Smaller branches were transformed into anastomosing abscess-like cavities filled with thick yellowish-green pus.

Microscopic Observations—The tumor showed large, wide, irregular glands with papillary infoldings that were lined by a high and markedly anaplastic columnar epithelium. These glands extended throughout the duodenal wall, growing along the lymph vessels. There was an intensive inflammatory reaction in the form of leukocytic and plasmocellular infiltrations.

In the liver, the periportal tissue was much increased and contained dense accumulations of leukocytes and large lipophages and cells filled with golden brown pigment granules. Most of the cells of the liver appeared well preserved, except for areas of compression where the cellular accumulations bordered on the parenchyma.

Diagnosis—The following anatomic diagnosis was made: medullary carcinoma of the second portion of the duodenum, marked dilatation of the extrahepatic and intrahepatic bile ducts, and intrahepatic purulent cholangitis, diffuse serofibrinous peritonitis with chronic tumor of the spleen, brown atrophy and cloudy swelling of the liver and myocardium, serous atrophy of the epicardial fat tissue, bilateral hydrothorax and hydropericardium, fibrinous pleuritis of the right side and compression atelectasis of the right pulmonary lobe, confluent bronchopneumonia of the lower lobe of the left lung, cloudy swelling and cyst formation of the kidneys, decrease of lipid content of the suprarenal cortex, icterus levis, inflammatory hyperplasia of the peripancreatic and peribiliary lymph nodes, aqueous and gaseous distention and edema of the intestines.

CASE 4—History—F. O., a white man, aged 60, married, was admitted to the Cook County Hospital on June 9, 1927, complaining of indigestion, vomiting, loss of weight and weakness. He had enjoyed perfect health until about seven months previously, when he had vomited two or three hours after a meal. The vomitus was copious and green. The vomiting recurred every two or three days for a period of ten weeks, and appeared about two hours after meals. During this time the patient lost weight steadily and became weaker. He had been under medical treatment for an ulcer during this time. A gastro-enterostomy was performed later at one of the local hospitals, from which he was making an uneventful recovery, until, "after the wrong tray," pain suddenly developed in the umbilical region and lasted for about two hours. He left the hospital and a short time later entered Cook County Hospital. At this time, he had abdominal cramps that usually appeared after meals and were relieved by enemas. Throughout his illness, his appetite remained good, yet he lost 50 pounds (22.7 Kg). Dyspnea had been present since the onset.

Examination—The patient was fairly well developed, but markedly emaciated, and appeared to be quite sick. Tenderness and the suggestion of a mass in the epigastrium were noted. The stomach was dilated. There were visible peristaltic waves, with audible gurgling sounds. The ankles pitted on pressure. The other observations were normal. The urine was normal. Examination of the blood gave normal results. The Wassermann reaction was negative.

The following diagnosis was made: pyloric obstruction due to a malignant condition or adhesions, ulcer at the site of enterostomy, and a malignant condition of the bowel.

Course—The basal metabolic rate was plus 10. Roentgenograms showed "30 per cent gastric retention; the pyloric region appeared defective on the screen, the stomach was in a position too high to palpate satisfactorily. The bulb was not well visualized. Marked stasis, surging and dilatation of a peculiarly looped or circled duodenal curve including the first, second and part of the third portions was noted. Suggestion of delay or impediment in the third portion of the duodenum was presumed." One hour after an Ewald meal was given, 230 cc of the stomach contents showed free hydrochloric acid, 5, total acidity, 18. Seven hours after a motor meal was given, 170 cc was obtained by tube, few remains of the meal were present. The patient became progressively weaker and died on June 18.

Necropsy—Necropsy was performed by Dr. Jaffe.

Gross Observations—The stomach was moderately distended and adherent to the surrounding structures by adhesions. A gastrojejunostomy had been performed. The first portion of the duodenum was closed surgically. At about 10 cm from the stump, there was an irregularly round opening, surrounded by a hemorrhagic, soft, fungating, slightly pedunculated area 2 by 5 cm.

Microscopic Observations Microscopically, the tumor was a papillary adenocarcinoma

Diagnosis—The following anatomic diagnosis was reported by Dr Jaffe: huge, ulcerating, perforated carcinoma of the third portion of the duodenum, secondary generalized fibrinopurulent peritonitis with bilateral subphrenic abscesses, sero-fibrinous pleurisy of the left side, band of adhesions between the omentum and the laparotomy scar with partial strangulation of several small intestinal loops, ancient gastric resection with a functioning gastrojejunostomy, subacute splenic tumor, passive hyperemia of the lungs, atherosclerosis of the aorta and coronaries, chronic periappendicitis, moderate-sized adenoma of the prostate, diverticulum of the jejunum, multiple rectal polypi, icterus levis, anemia

INCIDENCE

In 1901, Rolleston⁶ stated that primary carcinoma of the duodenum is "decidedly rare." As recently as 1926, Cabot⁷ also remarked that it is "very rare." Even considerable variation in this respect, as shown particularly in table 3, obviously is not beyond expectation, yet from a compilation of statistics appearing in the literature, some degree of unanimity is apparent. Primary duodenal carcinoma is found in from 0.01 to 0.1 per cent of all postmortem examinations with the common figures being from 0.01 to 0.03 per cent (table 1). Our cases were found among a total (Cook County and Michael Reese Hospitals) of 10,876 necropsies, an incidence of 0.037 per cent.

If one studies the relation of this lesion to carcinomas in general, one finds that from 0.04 to 1.1 per cent are in the duodenum, more commonly from 0.2 to 0.4 per cent (table 2).

Of the relation of duodenal carcinoma to intestinal carcinomas, much may be said. Whereas as high an incidence as 26 per cent has been reported in the duodenums (Kohler⁸), its frequency is more commonly quoted as being from 1.5 to 4 per cent, with a low maximum, 5.7 per cent (Geiser⁹) (table 3). It is known that carcinoma occurs far less commonly in the small intestine than in the large. According to Brill's¹⁰ collected statistics (1904), only 2.5 per cent of intestinal carcinomas are in the small bowel, the duodenum and the ileum being involved with equal frequency. Rolleston,⁶ Bland-Sutton,¹¹ Jefferson¹²

6 Rolleston, H. D. Carcinomatous Stricture of the Duodenum, *Lancet* **1** 1121 (April 20) 1901.

7 Cabot, R. Case Records, Boston M. & S. J. **194** 267 (Feb. 11) 1926.

8 Kohler, quoted by Forgue, E., and Chauvin, E. *Rev. de chir.* **50** 470 (Dec.) 1915.

9 Geiser, J. F. Ueber Duodenalkrebs, *Deutsche Ztschr. f. Chir.* **86** 41, 1906.

10 Brill, N. E. Primary Carcinoma of the Duodenum, *Am. J. M. Sc.* **128** 824, 1904.

11 Bland-Sutton, J. On Cancer of the Duodenum and Small Intestine, *Tr. M. Soc. London* **38** 1 (Oct. 12) 1914.

12 Jefferson, G. Carcinoma of the Suprapapillary Duodenum Casually Associated with Preexisting Simple Ulcer. Report of a Case, and an Appendix of Thirty Collected Cases, *Brit. J. Surg.* **4** 209 (Oct.) 1916.

TABLE 1—Percentage of Cases of Primary Duodenal Carcinoma Found at Necropsy

	Necropsies	Duodenal Carcinoma	Percentage
Perry and Shaw Guy's Hosp Rep 50 171, 1893	17,652	4	0.020
Fenwick and Fenwick Cancer and Other Tumors of the Stomach, London, 1902	19,518	18	0.090
Maydl Ueber den Darmkrebs, Vienna, 1883	20,480	5	0.010
Nothnagel Spez Path u Therap 17 220, 1898	21,358	5	0.020
Zemann, quoted by Brill Am J M Sc 128 824, 1904	21,624	3	0.013
Muller, M Inaugural Dissertation, Berne, 1892	5,621	6	0.100
Deaver and Ravdin Am J M Sc 159 469, 1920	151,201	50	0.033
Schlesinger Wien klin Wchnschr 11 245, 1898	42,000	7	0.017
Rulp, quoted by Fergue and Chauvin Rev de chir 50 470, 1915	4,258	1	0.023
Tiemann Beitrage zur Pathologie und Statistik des Krebses, Kiel, 1900	3,350	2	0.060
Geiser Deutsche Ztschr f Chir 86 41, 1906	11,314	7	0.062
Meyer and Rosenberg	10,876	4	0.037

TABLE 2—Percentage of Duodenal Carcinoma Among Cases of Carcinoma in General

	Carcinoma in General	Duodenal Carcinoma	Percentage
Muller, M Inaugural Dissertation, Berne, 1892	521	6	1.10
Lubarsch Arch f path Anat 111 280, 1888	569	2	0.35
Brill Am J M Sc 128 824, 1904	4,675	15	0.30
Schlesinger Wien klin Wchnschr 11 245, 1898	3,583	7	0.20
Jefferson Brit J Surg 4 209, 1916			0.04
Rulp, quoted by Fergue and Chauvin Rev de chir 50 470, 1915	372	1	0.27
Tiemann Beitrage zur Pathologie und Statistik des Krebses, Kiel, 1900	478	2	0.40
Geiser Deutsche Ztschr f Chir 86 41, 1904	900	7	0.77

TABLE 3—Percentage of Duodenal Carcinoma Among Cases of Carcinoma of the Intestines

Authors	Carcinoma of Intestine	Duodenal Carcinoma	Percentage
Fergue and Chauvin Rev de chir 50 470, 1915	888	42	4.5
Leichtenstern, quoted by Brill Am J M Sc 128 824, 1904	770	33	4.3
Geiser Deutsche Ztschr f Chir 86 41, 1906	123	7	5.7
Bryant, quoted by Brill Am J M Sc 128 824, 1904	110	6	5.5
Muller, F, quoted by Kaufmann Lehrbuch der speziellen pathologischen Anatomie, 1922	123	5	4.0
Zemann, quoted by Brill Am J M Sc 128 824, 1904	165	5	3.0
Rulp, quoted by Fergue and Chauvin Rev de chir 50 470, 1915	35	1	2.9
Maydl Ueber den Darmkrebs, Vienna, 1883	100	2	2.0
Ewald, quoted by Syme Lancet 1 148, 1904	1,148	19	1.7
Nothnagel Spez Path u Therap 17 220, 1898	243	5	2.0
Schlesinger Wien klin Wchnschr 11 245, 1898	443	7	1.6
Jefferson Brit J Surg 4 209, 1916	4,177	34	1.5
Lichhorst Handb d spez Path u Therap 2 234, 1890	34	9	26.0
Judd Journal Lancet 39 159, 1919	1,846	5	0.27
Haussmann Etiologie et pathogenie du cancer de l'intestin, These de Paris, 1882	285	0	0
Meyer and Rosenberg (Cook County Hospital)	569	3	0.53

and Deaver and Ravdin,¹³ however, stated that the duodenum is the most common site for carcinoma of the small intestine. Brill¹⁰ was able to find no instance of primary jejunal carcinoma, but since his paper appeared its incidence has greatly increased. Lahey¹⁴ in 1915, Jefferson¹² in 1916 and Judd¹⁵ in 1919 reported on twenty-four cases of carcinoma of the small intestine, they found eleven cases in the jejunum, five in the duodenum, six in the ileum and two with multiple involvement. In 1925, Eusterman, Berkman and Swan¹⁶ found fifteen of thirty-nine carcinomas of the small intestine localized in the duodenum.

We endeavored to study this relationship from the clinical records available at the Cook County Hospital. As diagnostic criteria we accepted the following: (1) physical observations, only rectal or proctoscopic examinations were considered sufficiently accurate, (2) roentgen examination showing an irregular filling defect, in conjunc-

TABLE 4—*Incidence of Carcinoma in Various Parts of the Intestines*

Duodenum	3	Transverse colon	14
Duodenojejunal junction	1	Splenic flexure	19
Ampulla of Vater	3	Descending colon	4
Jejunum	3	Sigmoid colon	66
Obendorf tumor*	12	Rectum	365
Ileum	3	Ileum, cecum and ascending colon	1
Appendix	1	Ascending and transverse	1
Cecum	30	Cecum, ascending and hepatic flexure	1
Ileocecal	2	Transverse and splenic flexure	1
Ascending colon	8	Rectosigmoid junction	12
Hepatic flexure	5	Colon	4
Total			569

* Personal communication with Dr. Richard Litvendshl, taken from his unpublished reports.

tion with occult blood in the stool, (3) the surgeon's diagnosis based on the appearance at the time of operation, (4) biopsy report, (5) postmortem examination. Table 4 shows our observations.

Of 569 clinical cases of intestinal carcinoma, 3 were located in the duodenum, primarily, and 1 was at the duodenojejunal junction. If we disregard the latter the incidence in our series is 0.53 per cent.

13 Deaver, J. B. and Ravdin, I. S. Carcinoma of the Duodenum, *Am J M Sc* **159** 469 (April) 1920.

14 Lahey, F. H. Carcinoma of the Small Intestine, *Am J Surg* **62** 428 (Oct.) 1915.

15 Judd, E. S. Carcinoma of the Small Intestine, *Journal-Lancet* **39** 159 (April 1) 1919.

16 Eusterman, G. B., Berkman, D. M., and Swan, T. S. Primary Carcinoma of the Duodenum. Report of Fifteen Verified Cases, *Am J Surg* **82** 153 (July) 1925.

In addition to the cases previously cited and those in the tables, Rolleston,⁶ Deaver and Ravdin,¹¹ Cabot,⁷ Bibby and Stewart,¹⁷ Head,¹⁸ Pommay and Seille,¹⁹ Jefferson,¹² Letulle,²⁰ Geisei,⁹ Skillern,²¹ Pauchet and Luquet²² and Syme²³ contributed reports of single instances. Lewis and Morse²⁴ recently reported twelve cases.

ETIOLOGY

In the majority of cases, duodenal carcinoma makes its appearance without any recognizable cause. Males are more frequently attacked than females, the predominance varying with the author, the ratio being 3:1 according to Rolleston,⁶ or 8:5 according to Pic.²⁵ All of our patients were males.

Duodenal carcinoma usually occurs in late middle and advanced life, the average age being 52 years. The average age of our patients was 49, corresponding with that of Forgue and Chauvin.²⁶ It has been encountered as early as 16 years (Ewald²⁷) and as late as 80 (Perry and Shaw²⁸).

No racial predilection is notable.

In an attempt to elucidate the pathogenesis of this condition, many theories have been propounded. Geisei⁹ suggested two theories: 1. The condition is caused by irritation, a fold of mucosa becomes

17 Bibby, J. P., and Stewart, M. J. Primary Carcinoma of the First Part of the Duodenum with Secondary Involvement of the Common Bile Duct, *Lancet* **1** 525 (Feb. 21) 1914.

18 Head, G. D. Primary Carcinoma of the Third Portion of the Duodenum, *Am. J. M. Sc.* **157** 182 (Feb.) 1919.

19 Pommay, S., and Seille. Un cas de cancer de la quatrième portion du duodenum, *Ann. d'anat. path.* **2** 141 (March) 1925.

20 Letulle, M. Cancer colloïde du duodenum développé sur un ulcère simple, *Bull. Soc. anat. de Paris* **72** 721 (Oct.) 1897.

21 Skillern, P. G. Cancer of the Duodenum, Pancreas and Pylorus, *Internat. Clin.* **3** 158, 1914.

22 Pauchet, V., and Luquet. Cancer de la quatrième portion du duodenum, *Bull. Acad. de med., Paris* **97** 276 (March 1) 1927.

23 Syme, G. A. Carcinoma of the Duodenum, Resection, Recovery, *Lancet* **1** 148 (Jan. 16) 1904.

24 Lewis, J. W., and Morse, G. W. Primary Carcinoma of the Duodenum. Report of Twelve Proved Cases, Summary of Literature, *New England J. Med.* **198** 383 (April 12) 1928.

25 Pic, A. Contribution à l'étude du cancer primitif du duodenum, *Rev. de med.* **14** 1081 (Dec.) 1894, **15** 56 (Jan.) 1895.

26 Forgue, E., and Chauvin, E. Le cancer primitif et intrinsèque du duodenum, *Rev. de chir.* **50** 470 (Dec.) 1915.

27 Ewald, C. A. Ein Fall von Atrophie der Magenschleimhaut mit Verlust der Salzausscheidung. *Ulcus carcinomatosum duodenale*, *Berl. klin. Wchnschr.* **23** 527 (Aug. 9) 1886.

28 Perry, E. C., and Shaw, L. E. On Diseases of the Duodenum, *Guy's Hosp. Rep.* **50** 171, 1893.

chronically irritated by the duodenal contents. 2 In the area contiguous to the papilla of Vater, there is a conflict of two types of epithelial cells, with a resultant proclivity to carcinomatous degeneration, which explains the greater frequency of carcinoma at this part of the duodenum. Several predisposing factors based on the anatomic relations of the duodenum were discussed by Forgue and Chauvin.²⁶ The projection of the papilla into the lumen with irritation by food received consideration. The fixation of the duodenum by the parietal peritoneum, the four flexures and the difficulty in adapting itself to the contents were conceived as factors. Likewise, the duodenum was said to be the most dilated portion of the small intestine and hence to favor stasis and consequent irritation.

Chronic duodenal ulcer has been thought by some writers and investigators to predispose to the development of carcinoma, and while this relationship must be considered, *sub judice*, the consensus is negatory. Peiry and Shaw²⁸ reported five cases (including one observed by Sidney Coupland) purported to have developed on the basis of an ulcer. Letulle²⁹ and Geiser⁹ each reported a case. Ewald,²⁷ Schrotter,²⁹ Mackenzie³⁰ and Eichhorst³¹ reported single instances (collected with Letulle's by Nattan-Larrier³²). Jefferson¹² collected nineteen additional cases appearing in the literature and added one of his own. After critically reviewing the clinical and pathologic accounts, we must conclude, as Jefferson did, that "some are very doubtful." In 1900, Menetrier³³ investigated the relationship and concluded that a hyperplastic cellular reaction bordering on adenomas was produced near the ulcer and slowly developed into carcinoma. One would expect, then, to find carcinoma more frequently in the first portion of the duodenum, the common site of ulcer, whereas actually, the second portion is more commonly involved. Because of the rarity of ulcer-carcinoma and the uncertainty that surrounds any attempt to correlate the two, it is our belief that they may be coincidental.

By virtue of their irritation to the duodenum, gallstones have been mentioned as important in the explanation of the more frequent involvement of the second portion of the duodenum. In this respect, an interesting paradoxical observation was noted in Geiser's⁹ study. Although cholelithiasis occurs more frequently in women and ulcer

29 Schrotter, L. *Aerztl. Ber. d. k. k. allg. Krankenh. zu Wien*, 1886, p. 27.

30 Mackenzie, H. W. G. *Duodenal Ulcer, Obstruction of Common Bile-Duct, Jaundice, Malignant Disease of Liver, Intestinal and Cerebral Hemorrhage*, St. Thomas's Hosp. Rep. 1890-1891, **20**: 341, 1892.

31 Eichhorst, H. L. *Handb. d. spez. Path. u. Therap.* **2**: 234, 1890.

32 Nattan-Larrier. *Les cancers du duodenum*, *Gaz. d. hop.* **72**: 1291 (Dec. 2) 1899, **72**: 1311 (Dec. 7) 1899.

33 Menetrier, quoted by Forgue and Chauvin (footnote 26).

more often in men, carcinoma of the second portion of the duodenum occurred more frequently in men and that of the first portion more frequently in women

Syphilis has been considered as a factor, but although occurring in the case of Lewis and Moise²⁴ and Curtis and Surmont²⁵ and in case 1 of our group, it is probably of no significance

PATHOLOGY

Carcinomas of the duodenum are most often primary in origin. They are thought to arise from the mucosa, Brunner's glands (Oltz), aberrant pancreatic tissue (Cohnheim) or aberrant stomach tissue (McGuire and Cornish³⁵). In commenting on their origin, Bland-Sutton remarked that any theories implicating aberrant pancreatic tissue or Brunner's glands "belong to the domain of fiction."

Usually they are cylindrical cell adenocarcinomas that have a tendency to encircle the duodenum, producing stenosis with proximal dilatation, muscular hypertrophy and chronic catarrhal inflammation. Some of them are spherical cell adenocarcinomas, taking the form of soft excrescences or of deep ulcers with elongated edges and fungated bases (Head¹⁸), these being difficult to distinguish from carcinoma arising in the ampulla, pancreatic duct or pancreas. They may be scirrhous, medullary or colloid (Bill¹⁰). They ulcerate frequently and occasionally perforate, producing peritonitis (case 4). Metastases appear late and are found in the liver, regional lymph nodes, pancreas and lungs and less commonly in the peritoneum, gallbladder, supraclavicular glands (case 2) and bones. Eichhoist³¹ reported metastases to the bone marrow of the sternum. Geiser⁹ called attention to their tendency to produce metastases in the liver and regional lymph nodes with compression of the common bile duct, thereby simulating carcinoma of the pancreas.

Pic²⁵ divided them into three types, namely (1) parapyloric (*formesus-vaterienne*), (2) periampullary and (3) prejejunal (*forme sous-vaterienne*). The most common type is the periampullary, the most infrequent, the prejejunal.

The parapyloric type usually encircles the duodenum, producing stenosis with proximal dilatation, insufficiency of the pyloric ring and gastric dilatation. Its relation to peptic ulcer has already been discussed. Morrison and Feldman³⁶ reported an interesting case of primary para-

34 Curtis, F, and Surmont, H. Cancer duo pylore d'origine duodénale chez un syphilitique, *Arch d mal de l'app digestif* **13** 24 (Jan) 1923

35 McGuire, E. R., and Cornish, P. G. Carcinoma of the Duodenum, *Am J Surg* **72** 600 (Nov) 1930

36 Morrison, T. H., and Feldman, M. Autopsy Report of a Case of Primary Carcinoma in a Duodenal Diverticulum *Am J Clin Med* **5** 326 (Oct) 1926

pyloric carcinoma that arose in a diverticulum and metastasized to the liver. They stated that this is the only case in the literature. No additional accounts have appeared since theirs.

The periampullary type usually arises in or about the papilla as an infiltration about the size of a walnut or cherry, it tends to encircle and extend along the duodenum (Nothnagel³⁷). It is difficult to differentiate this type from carcinoma of the ampulla (case 1). The latter, however, is sharply circumscribed about the papilla (Nothnagel³⁷). Attention is called to the difficulty of recognition of the true primary origin of carcinoma of the second portion of the duodenum by histologic examination. The papilla that may be the site of a primary tumor may reveal histologic evidence of carcinoma along the duct, but this may fail to aid in differentiation. Geiser made the point that a lesion originating from the papilla may show carcinomatous changes along the lumen of the duct, but even this is not positive for the duct may be secondarily involved from the primary duodenal lesion. Obstruction to the flow of biliary and pancreatic juices is produced, leading to dilatation of the bile ducts and capillaries, distention of the gallbladder, increase in the size of the liver with subsequent increase in connective tissue and cirrhosis, dilatation of the pancreatic ducts and pancreatic atrophy (case 1). With ulceration of the tumor, the resultant signs and symptoms of biliary obstruction and pancreatic disease disappear (case 1). Occasionally, death may follow erosion of the blood vessel (case 1). In other cases infection develops in the biliary tract, which leads to a suppurative cholangitis with intrahepatic abscesses (case 3).

The prejejunal form is most often broad, flat and ulcerated. Stenosis develops, with dilatation of the proximal segments, namely, the duodenum, the pyloric ring and the stomach.

SYMPTOMS

The onset of the condition is variable. It may be sudden or insidious. Most commonly, it manifests itself by the appearance of nausea, progressive loss of appetite and weight, gaseous eructations, heartburn, jaundice or epigastric discomfort (fullness or dull pain), which usually occurs two or three hours after meals and is relieved by the use of soda or by vomiting. Sometimes the patient's attention is first arrested by the perception of a tumor mass in the epigastrium, the right hypochondrium or the umbilical region. At other times hematemesis is the first symptom. Rarely, progressive asthenia, emaciation and swelling of the abdomen from ascites are first noted.

³⁷ Nothnagel, quoted by Ewing, J. *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1919, p. 641.

With the progress of the disease, pain usually becomes more prominent. It may be burning or intermittent and cramplike, it usually appears in the epigastrium or the right hypochondrium two or three hours after meals and is relieved by vomiting. Yet there may be no relation to meals. This pain has been explained in various ways, namely, (1) contraction of the stomach or intestine against an obstruction, (2) compression of the celiac axis by the tumor, (3) distention of the liver or gallbladder from biliary stasis.

Vomiting appears with the development of the obstruction. At first it is noted from the one-half to one hour after eating. Later, it occurs immediately after eating. Still later, it becomes less frequent, that is, once daily, but is abundant. Ultimately, owing to the ulceration of the tumor and relief from the obstruction, it may cease. Repeated vomiting results in an increased thirst, oliguresis and dehydration.

Jaundice, a common symptom, usually increases in intensity. It is due to an obstruction at the ampulla of Vater by the tumor or by edema of the papilla, to hepatic metastases or to compression of the common bile duct by the lymph nodes. However, it may become intermittent, consequent to ulceration of the tumor.

Constipation is common, owing either to progressive intestinal obstruction or to recurrent vomiting. At times it may alternate with diarrhea. The stools may be clay-colored, black or normal.

Fever is usually absent until late, when it is often due to ulceration of the tumor.

In some respects the clinical picture varies with the part of the duodenum affected. The parapyloric type usually does not produce icterus. It simulates pyloric obstruction so closely that it is almost impossible to differentiate the two conditions. The prejejunal type differs from the parapyloric by the presence of bile and pancreatic ferments in the vomitus, the differentiation having been first made by Chomel.⁴ Pommay and Seille¹⁹ pointed out the longer latent period during which general symptoms of malignancy dominate. The periampullary type simulates the parapyloric when the tumor is located above the papilla, and the prejejunal when the tumor is below the papilla. When the tumor is located at the papilla, a progressive, painless, obstructive and sometimes intermittent jaundice results, with few if any gastro-intestinal symptoms. Biliary and pancreatic obstruction, ascending cholangitis and hepatic abscesses are more likely to develop here. In the event of pancreatic obstruction, the stools become large, pale, fatty and offensive.

PHYSICAL EXAMINATION

Our attention was directed to the pallor and emaciation and, in instances of recurrent vomiting, to the dehydration. Icterus is com-

monly present. The abdomen is flat and soft, epigastric distention is rarely detected. Peristaltic waves may be visible across the upper part of the abdomen, and sometimes the outlines of a dilated stomach and duodenum may be seen or percussed. Frequently, a tumor mass may be felt, and while it is usually located in the epigastrium to the right of the midline, it may be found in the right hypochondrium or in the region of the umbilicus. The tumor mass is hard, irregular and, when perapyloric, mobile. The perampullary and prejejunal forms show little if any mobility. The gallbladder is usually distended, tense and easily delimited. The liver is commonly enlarged, firm, smooth and not tender. Enlarged supraclavicular glands are occasionally found. In the advanced stages, ascites, metastatic peritoneal implantations and a nodular liver may be revealed. Gastric succussion is sometimes elicited.

LABORATORY OBSERVATIONS

In a large proportion of cases, the contents of the stomach show a diminution or absence of free hydrochloric acid. Sometimes the gastric acidity is normal. It is not common to find blood, except in advanced cases with malignant ulceration associated with insufficiency of the pylorus. Of the greatest diagnostic import is the presence of bile and trypsin in all cases of obstruction below the papilla. Gastric retention is encountered in the later stages of all duodenal carcinomas.

The stools vary in character, depending on the presence or absence of ampullary obstruction. In the former, they are acholic, and with the progress of pancreatic degeneration they become offensive and bulky, with undigested meat fibers and starch and an excess of neutral fats. Occult blood is found in all of them.

The urine contains an increased amount of indican and creatinine. Bile is detected in cases of biliary obstruction, with pancreatic changes dextrose may be found.

The blood shows varying degrees of anemia, with a greater decrease in the hemoglobin content as compared with the erythrocytic count, whereas leukocytosis is common as part of the picture of anemia, a further increase may be noted the result of malignant ulceration. The differential formula shows an increase in polymorphonuclear neutrophils. Hyperglycemia may be present and it is usually associated with advanced pancreatic changes. In instances of repeated vomiting, elevation in the carbon dioxide-combining power and lowering of the chlorides may be demonstrated (alkalosis). The blood urea is increased.

ROENIGEN EXAMINATION

The site of the malignant process is revealed, and if the process has advanced to the point of producing stenosis, proximal dilatation of the duodenum and stomach and gastric hypomotility may be observed.

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COMPLICATIONS

Secondary growths are common in the late stages especially in the liver, regional lymph nodes and adjacent structures. Ascites may develop from peritoneal carcinosis. Forgue and Chauvin²⁶ referred to the occurrence of a duodenocolic fistula that resulted from adhesions to the colon and produced diarrhea.

Geiser⁹ observed a case of compression of the ureter with hydronephrosis. Often a suppurative cholangitis with intrahepatic abscesses and empyema of the gallbladder is seen in the terminal stages. The primary growth may ulcerate, perforate and produce a peritonitis (case 4) with subphrenic, retroperitoneal or peri-intestinal abscesses. Phlebitis of the portal vein, the inferior vena cava, the iliac and the hypogastric and femoral veins, with corresponding ascites or edema of the lower extremities, or both, has been reported. A sudden severe hemorrhage with hematemesis and melena from erosion of a large vessel may terminate the picture (case 1).

COURSE

The course is usually chronic, lasting from three to eighteen months, the average being seven months after the first appearance of symptoms. The anemia, asthenia, emaciation and cachexia progressively increase, commonly, oft-repeated vomiting eventuates. Death has been known to occur in a few days, rarely later than after two months, in the cases in which there is severe vomiting and in which surgical intervention is not attempted. Death may be the result of great emaciation and gradual exhaustion, intercurrent infection, especially bronchopneumonia, peritoneal complications or hemorrhage.

DIAGNOSIS

The diagnosis is most difficult. Geiser⁹ said that the diagnosis of the parapyloric type has not been made by physical examination. Owing to the rarity of carcinoma of the duodenum, it is seldom suspected. A person who is well past middle age and who gives a history of epigastric distress of relatively short duration is more apt to be suspected of having a carcinoma of the stomach than a carcinoma of the duodenum. Forgue and Chauvin²⁶ noted that in only two of forty-five cases was the true diagnosis suspected. The absence of a distinctive symptom-complex is probably equally important as a cause for failure in diagnosis. Such symptoms as pain in the epigastrium after meals, vomiting and other evidence of retention speak for stenosis—pyloric or duodenal. The presence of greater mobility of the duodenum than of the pylorus is of little value in differentiating parapyloric duodenal carcinoma from

carcinoma of the pylorus The claim of some that free hydrochloric acid is present in the gastric contents in cases of parapyloic carcinoma (duodenal) as contrasted with achlorhydria in carcinoma of the pylorus (gastric) is disputed by Geiser who asserted that parapyloic carcinoma (duodenal) becomes noticeable only when it has resulted in gastric dilatation, and by that time the gastric acidity is nil, as in carcinoma of the pylorus

The periampullar type of duodenal carcinoma, which is the most common form, causes even greater difficulties in diagnosis The gradual development of a symptom-complex, such as progressive jaundice, enlargement of the gallbladder, vomiting, acholic stools and the absence of tryptic digestion, makes the differentiation from carcinoma of the head of the pancreas impossible In such cases, roentgen evidence is also of little aid, gallstones are probably easily differentiated, but such conditions as carcinoma of the papilla, carcinoma of the gallbladder and chronic interstitial pancreatitis can be diagnosed with certainty only at operation and on histologic examination Of some clinical value may be the fact that carcinoma of the biliary tract, as well as carcinoma of the papilla, tends to produce early metastases, whereas the periampullar type of duodenal carcinoma produces metastases late Carcinoma of the papilla is more likely to be associated with an intermittent jaundice, while in carcinoma of the duodenum the jaundice is of the obstructive type and diminishes only with extensive ulceration of the tumor

The prejejunal variety of duodenal carcinoma is marked by gastric dilatation, a variability in gastric acidity, associated presence of bile and pancreatic juices and trypsin in the gastric contents Attacks of acute abdominal pain and severe vomiting are not uncommon The foregoing symptomatology calls for the differentiation from carcinoma of the jejunum and carcinoma of the pylorus (stomach) The roentgen rays should be of value in differentiating definitely from the latter Further, free hydrochloric acid is more likely to be present in the prejejunal type of duodenal carcinoma than in carcinoma of the pylorus In carcinoma of the pylorus there is usually no bile, trypsin or pancreatic juice Occasionally in carcinoma of the pylorus with insufficiency of the pyloric ring, there is a regurgitation of bile and pancreatic juice (Geiser⁹), thus making the differentiation from prejejunal carcinoma most difficult

The absence of marked abdominal distention, associated with a symptom-complex of intestinal obstruction, points with greater probability to a lesion being located in the small than in the large bowel Likewise, the vomiting of feculent material is ascribed by Geiser⁹ as being more likely in the jejunum than in the duodenum

It is important to bear in mind the possible confusion of carcinoma of the duodenum with an ulcer of the duodenum in very old persons. This is especially true in duodenal ulcer with obstruction. Like carcinoma of the stomach, carcinoma of the duodenum has a history of relatively short duration. It is not an uncommon experience to observe acute ulcers of the duodenum in persons past 50 or 60 years of age. Some of these, it is true, are not acute, but have a chronic history. In an analysis of thirty-eight cases of duodenal ulcer³⁸ in persons past 50, the following data were noted relative to duration. In eleven cases, the duration was from ten to seventeen years, in six cases, from two to five years, in seven cases, from one month to one year, in nine cases, from two to nine weeks, in three cases, no definite history, and in one, twenty-six years. The occurrence in sixteen instances of duodenal ulcer in persons past 50 with a history of duration varying from two weeks to one year is significant enough to direct attention to the possibility of a malignant process. The general tendency of the clinician is to regard the person past middle age with a history indicating ulcer as having either a gastric ulcer or a gastric carcinoma. While these are unquestionably the most likely possibilities, some of the cases may prove to be duodenal carcinoma (case 4).

While recognizing the difficulty of diagnosis of duodenal carcinoma both clinically and histologically, we raise the question whether careful study may not reveal an increasing number of duodenal carcinomas. Analogous to this is the now well recognized fact that the majority of the so-called pyloric stenoses are on the duodenal side. It is also interesting to note the careful studies of Nagel,³⁹ who reported slight involvement of the duodenum in five of fourteen cases of cancer of the pylorus.

Lest we be misunderstood, we wish to emphasize the difficulties of definite diagnosis of primary carcinoma of the duodenum and the necessity of careful, critical, histologic study of all tissues. Thus in a review of the cases at Michael Reese Hospital, we encountered one case which on histologic examination showed malignant infiltration of a duodenal scar. The gross impression of the pathologist was that of an old scar from an ulcer. Histologic examination of the infiltrated scar revealed definite evidence of carcinoma. The pathologist was of the opinion that the mother tissue was that of the gallbladder. The liver and bile passages showed no evidence of carcinoma. We cite this instance, because it shows the necessity of the histologic study of scars, and also because it emphasizes that the malignant process, though in

38 From the Stomach Study Group of the Michael Reese Hospital

39 Nagel, G. W. Unusual Conditions in the Duodenum and Their Significance, *Arch Surg* **11** 529 (Oct) 1925

the scar, may not be primary in the duodenum. We likewise direct attention to the fact that resection is the method of treatment for duodenal ulcer in relatively few clinics. We are of the opinion that if this procedure is followed and a greater number of scars of duodenal ulcers are subjected to histologic study, the incidence of duodenal carcinoma may be found to be greater.

In like manner, we question whether a certain number of cases that are diagnosed at operation as carcinoma of the head of the pancreas and that are not followed by later careful histologic study may not have their origin as a primary duodenal carcinoma. It occurs to us that in well advanced cases of primary duodenal carcinoma in which it is so difficult to determine the primary focus it is conceivable that the traditional rarity of a duodenal carcinoma directs the examiner's mind away from the duodenum, and therefore the diagnosis is that of a primary lesion in the adjacent structures, such as the pancreas, the papilla or the gallbladder.

TREATMENT

Medical treatment can be of little value except so far as it may be directed toward symptomatic relief. As metastases do not appear until late, surgical intervention is advocated as the method of predilection. The type of operation, however, will depend on the presence or absence of jaundice or metastases. In instances without the aforementioned complications, wide excision is recommended. Syme²³ resected a carcinoma of the third portion of the duodenum, the patient was in good condition when seen one month later. Pauchet and Luquet²² resected the fourth portion of the duodenum for carcinoma. This patient was able to resume his daily labors a short time later. Dewis and Morse²⁴ reported a case in which a posterior gastrojejunostomy was performed for suspected nonmalignant duodenal ulcer. Two and a half months later, the ulcer was considered malignant, and a wide resection was performed. The patient was alive and well one year and five and a half months after the first admission. With the development of metastases, or if the general condition is too poor to permit resection, a palliative posterior gastro-enterostomy should be performed. When duodenal carcinomas are associated with jaundice, such as in the perampullary form, they are best treated by preliminary cholecystogastrostomy, duodenostomy or enterostomy, followed later by either posterior gastro-enterostomy or resection, depending on the exigencies of the cases.

For discussion and descriptions of the technic involved in surgical intervention in the perampullary form, the excellent papers of

Halsted,⁴⁰ Mayo⁴¹ Kausch⁴² Lewis⁴³ Abell⁴⁴ and Cohen and Colp⁴⁵ are mentioned

CONCLUSIONS

Four cases of primary carcinoma of the duodenum are reported. Emphasis is placed on the difficulty of clinical recognition and of the necessity of carefully studying, clinically as well as histologically, all cases of duodenal stenosis. A critical analysis may reveal a greater incidence of primary duodenal carcinomas.

55 East Washington Street

40 Halsted, W. S. Contributions to the Surgery of the Bile Passages, Especially of the Common Bile Duct, Boston M. & S. J. **141** 645, 1899.

41 Mayo, W. J. Cancer of the Common Bile Duct. Report of a Case of Carcinoma of the Duodenal End of the Common Duct with Successful Excision, St. Paul M. J. **3** 374, 1901.

42 Kausch, W. Die Resektion des mittleren Duodenum. Eine typische Operation, Zentralbl. f. Chir. **36** 1350, 1909. Das Karzinom der Papilla duodeni und seine radikale Entfernung, Beitr. z. klin. Chir. **78** 439 (May) 1912.

43 Lewis, R. N. Cancer of the Ampulla of Vater, Surg. Gynec. Obst. **32** 543 (June) 1921.

44 Abell, I. Carcinoma of the Papilla of Vater, South M. J. **17** 24 (Jan.) 1924.

45 Cohen, I., and Colp, R. Cancer of Periapillary Region of Duodenum, Surg. Gynec. Obst. **45** 332 (Sept.) 1927.

ACUTE ISOLATED MYOCARDITIS

WITH REPORT OF A CASE [†]

CLARENCE E DE LA CHAPELLE, M D

AND

IRVING GRAEF, M D

NEW YORK

Recently, Scott and Saphir ¹ reported two cases of acute isolated myocarditis, which were the first to be recorded in the American literature. They mentioned the reports of thirty-six other cases with post-mortem observations recorded in the Continental literature since 1888, when Steffen ² described two cases of acute myocarditis which probably fall into this classification. Fiedler, ³ however, in 1890 was the first to give a clear description of the disease, and it is his name that has served as an eponym since.

There are many synonyms in use in labeling this type of lesion. A few of the terms used by previous authors are "interstitial," "circumscribed," "diffuse," "isolated," "idiopathic" and "primary," singly or in combination. The terms refer to an inflammatory lesion of the myocardium alone, which is associated with a distinctive clinical and pathologic picture.

Sellentin ⁴ was the first to name the disease isolated myocarditis because, as a rule, changes are not found in other parts of the heart or in other organs.

It has been noted by practically all authors that the outstanding clinical feature is progressive myocardial insufficiency which may be rapid or gradual. The striking feature in most of the cases has been the lack of association with antecedent infectious diseases, valvular heart disease or hypertension.

Thirty of the previously recorded cases were tabulated by Scott and Saphir ¹. Of these, ten occurred in males and thirteen in females, the authors added their two cases to the male group. Information as to the

[†] Submitted for publication, Sept. 20, 1930.

¹ From the Third (New York University) Medical Division and the Pathological Laboratories, Bellevue Hospital.

1 Scott, R. W., and Saphir, Otto. Acute Isolated Myocarditis, *Am Heart J* **5** 129 (Dec.) 1929.

2 Steffen, A. Zur akuten Myokarditis, *Jahrb f Kinderh* **27** 223, 1888.

3 Fiedler, A. Ueber akute interstitielle Myokarditis, *Centralbl f inn Med* **21** 212, 1900.

4 Sellentin, L. Akute isolierte interstitielle Myokarditis, *Ztschr f klin Med* **56** 298, 1904.

sex of the other seven patients was not available. Incidence as to age in their table indicates a distribution from the first to the eighth decades. Ten, or more than one third of all of the cases previously recorded with data on the age of the patients (total twenty-eight, including the two cases reported by Scott and Saphin), occurred in the third decade.

Evidence of the common infections recognized as the usual cause of heart disease was lacking in most of the cases, and a clearly defined etiologic agent has not been demonstrated to the present time. However, some authors associated the changes found with certain infections e. g., influenza, carbuncles, gonorrheal urethritis, pneumonia, infected wounds, cellulitis and rheumatism. Two cases were associated with burns.

Necropsy observations in most of the cases have revealed enlargement of the heart, with marked dilatation of the chambers. The muscle of the heart has been variously described as pale, swollen and soft, sometimes as friable, with irregular streaks and spots varying in size and color scattered throughout. An observation common to all has been the absence of pericardial and endocardial lesions. Intracardiac mural thrombi have been found frequently.

Gallavardin⁵ recently added another case to the literature. He observed progressive myocardial insufficiency, associated with idiopathic cardiac enlargement without signs of valvular disease, in a white woman, 37 years old. The patient's history was not important. The clinical course lasted six months, and the diagnosis of subacute primary myocarditis was made before death. At necropsy the heart was enlarged, more dilated than hypertrophied, and weighed 420 Gm. On section, there were characteristic changes with considerable fibrosis confined to the wall of the left ventricle. Histologic changes were similar to the recorded observations.

The first histologic description was made by Schmorl,⁶ who examined Fiedler's cases. Microscopically, all authors gave the description of diffuse infiltration of the myocardium with cellular elements of different types. Some noted chiefly polymorphonuclear leukocytes, occasional round cells and a few eosinophils. In his case, Saltykow⁷ described the infiltration as consisting of polymorphonuclear leukocytes, lymphocytes, fibroblasts, plasma cells, mast cells, wandering endothelial cells and eosinophils, as well as cells that he thought were degenerating forms of muscle cells. The latter were also found forming giant cells.

5 Gallavardin, L., and Gravier, L. Un nouveau cas de myocarde subaiguë primitive à lésions interstitielles, *Arch d mal du cœur* **22** 379, 1929.

6 Schmorl, L., in discussion of Aschoff, L. *Verhandl d deutsch path Gesellsch* **8** 46, 1904.

7 Saltykow, S. Ueber diffuse Myokarditis, *Virchows Arch f path Anat* **182** 1, 1905.

Aschoff⁸ recorded a case that he felt was of rheumatic origin combined with some other agent. Aschoff's case showed eosinophils, plasma cells, lymphocytes and a few fibroblasts, with slight necrosis of the muscle fibers. Other authors described other histologic pictures. All agreed that the primary changes are in the interstitial tissues, the parenchyma being inconstantly involved. Gallavardin⁵ called attention to the possibility that the interstitial lesions are secondary to parenchymal necrosis, and indicated that the term "interstitial" refers to the end-stage of the lesion.

The following case is reported to add another example of what appears to be Fiedler's myocarditis to the small group already recorded.

REPORT OF CASE

History—A M, a white man, aged 21, born in Argentina, a laborer, was admitted to Bellevue Hospital, Third (New York University) Medical Division, on Jan. 25, 1930, complaining of pain in the chest and dyspnea of about two weeks' duration. His family history was irrelevant. He did not recall having had any of the diseases of childhood. He had had frequent colds, but at no time had he had polyarthritis. He said that he had not had venereal disease.

In May, 1929, while riding a bicycle, the patient suddenly and without premonitory symptoms fell (unconscious?). He was removed to a hospital, where it was found that he had hemiplegia. A diagnosis of hysteria was also made. In this hospital, Wassermann tests of the blood and spinal fluid were reported to be negative, the colloidal gold curve was also negative. Other laboratory tests also gave negative results. On discharge four days later, he was able to use his left arm and leg to a slight extent. His condition improved gradually, and by August he was practically normal, except for slight weakness of the left hand.

About Jan. 1, 1930, the patient began to cough. He consulted a physician who gave him medicine and instructions to return in a week. The cough grew progressively worse. During the second week of the illness, he expectorated bloody sputum and began to experience pain in the lower right side of the chest. At this time he noticed shortness of breath on slight exertion. He returned to his physician, who strapped his chest. The cough, blood-tinged sputum, shortness of breath, pain in the chest and weakness persisted, and the patient went to bed. After a week the patient entered Bellevue Hospital because of continued dyspnea and pain in the chest. At the time of admission, the productive cough had practically disappeared. He had not felt feverish, lost weight, sustained a chill or experienced night sweats at any time during his illness, but he had noticed swelling of his feet during the week previous to admission.

Examination—The patient appeared to be chronically ill, but well nourished. He was slightly dyspneic and orthopneic, and he had a café-au-lait color. There was cyanosis of the lips and finger tips. His pupils reacted to light and in accommodation. No petechiae were seen in the conjunctivae, the sclerae were icteric, the fundi oculi presented the slate appearance of cyanosis, the retinal vessels were normal, and there was no evidence of hemorrhages or exudates. The pharynx and tonsils were hyperemic, but no pus could be expressed from the latter. The

⁸ Aschoff L. Zur Myokarditisfrage, Verhandl. d. deutsch. path. Gesellsch. 8: 46, 1904.

tonsillar lymph nodes were palpable on the right side. The teeth were in fair condition. The thyroid was not visible or palpable. There was no clubbing of the fingers.

Examination of the heart revealed pulsating veins in the neck; one of the superficial veins of the left arm could be seen to pulsate. The apical beat of the heart was visible and palpable in the sixth space, 14 cm from the median line, which point was at the anterior axillary line. A 2 meter roentgenogram of the heart, taken five days after admission, showed marked enlargement in the transverse and long diameters. The first sound at the apex of the heart was of poor muscular quality, the sounds at the base were faintly audible. The rhythm was regular, the rate was 92 a minute, and the radial pulse was small. The systolic blood pressure was 105 mm, the diastolic, 82 mm.

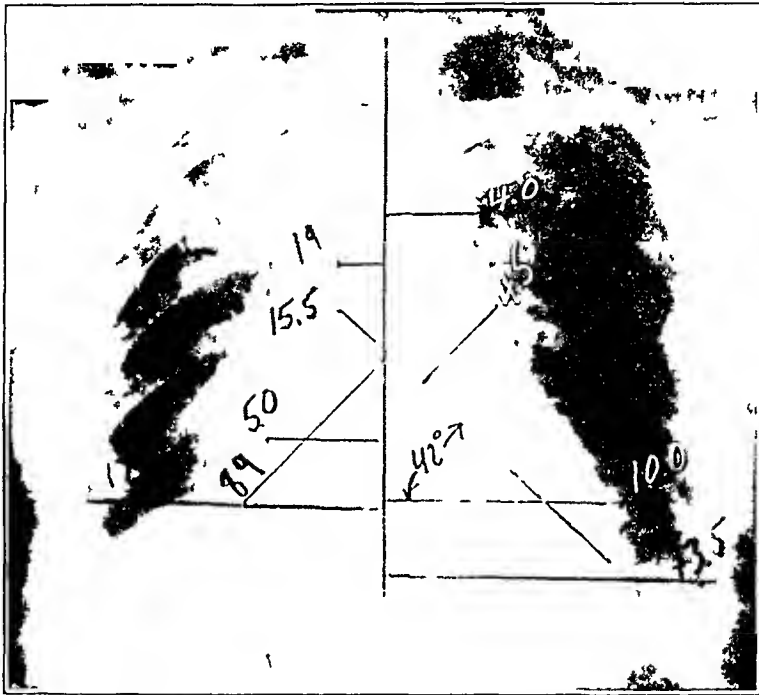


Fig 1—Roentgenogram (2 meters) of the heart taken nine days before death, showing marked enlargement of the cardiac outline.

The respiratory rate was 32 a minute. There were signs of fluid over the area of the lower lobe of the right lung, with crepitant and subcrepitant râles and dulness above the eighth rib posteriorly. The edge of the liver was palpable 3 cm below the costal margin, it was tender, but did not pulsate. The spleen was not palpable. There was no evidence of ascites. Both lower extremities presented slight edema. The superficial and deep reflexes were active, and there were no abnormal reflexes.

On admission, examination of the blood showed leukocytes, 10,400, polymorphonuclears, 79 per cent, lymphocytes, 20 per cent, transitionals, 1 per cent, red cells, 3,700,000, and hemoglobin, 70 per cent. Another leukocyte count, taken four days later, showed 17,200 leukocytes, with 92 per cent polymorphonuclears and 8 per cent lymphocytes. The Wassermann reaction of the blood was negative. Blood cultures taken on two different occasions yielded no growth. The systolic blood pressure never exceeded 112 mm, the diastolic pressure ranged between

82 and 92 mm Four electrocardiograms, taken on different days during the last week, revealed prolongation of the P-R interval (from 0.20 to 0.24), there was a complete intraventricular block, low voltage in all three leads and normal sinus rhythm Examination of the sputum revealed an unclassified pneumococcus On admission, the urine was normal, subsequent urinalysis revealed a slight albuminuria and the appearance of numerous hyaline and finely granular casts, an occasional red blood cell was found on one occasion the day before death Chemical analysis of the blood, performed two days after admission, showed nonprotein nitrogen, 64 mg, and sugar, 119 mg per hundred cubic centimeters Three days before death, the nonprotein nitrogen was 100 mg and the creatinine 4.7 mg per hundred cubic centimeters

Clinical Course—The temperature ranged between 98 and 100 F, the pulse rate between 68 and 100 a minute Thoracentesis was performed two days after admission and yielded 80 cc of clear straw-colored fluid, with a specific gravity of

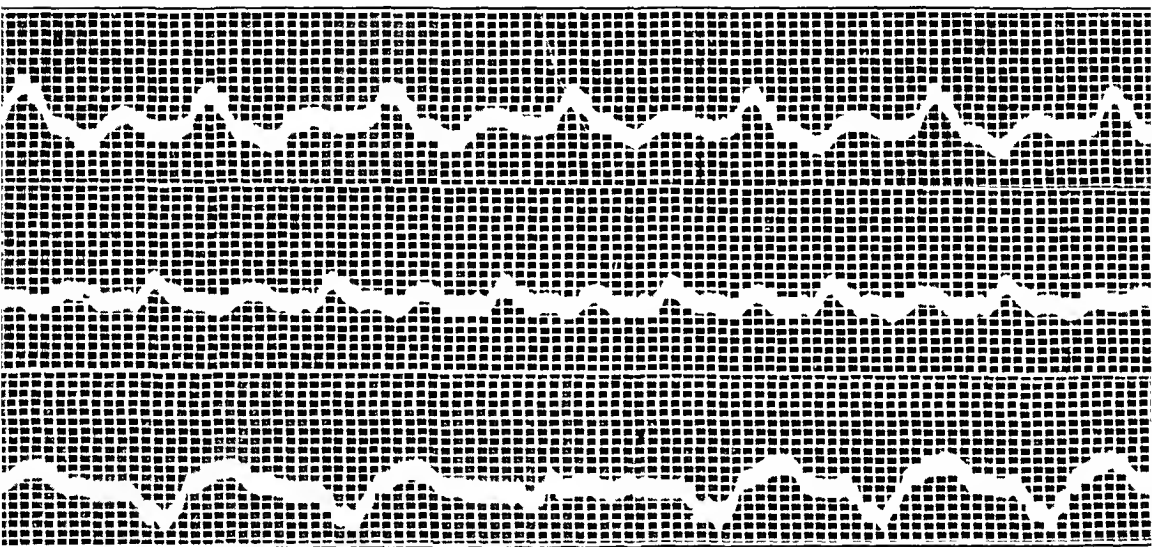


Fig 2—One of four similar electrocardiograms obtained between January 30 and February 5 First stage A-V block, complete intraventricular block, string resistance, 4,000 ohms, resistance of patient, 2,000 ohms, rate, 90, P-R interval, 0.20, QRS, 0.18, T₁ and T₂ inverted, and sinus arrhythmia

1 008 The cell count was 1,940, the differential count being comprised chiefly of lymphocytes and endothelial cells No tubercle bacilli were found The signs in the lower lobe of the right lung persisted A roentgenogram of the lungs showed irregular consolidation in this field

The patient progressively gained weight, with an increasing edema of the lower extremities and the left arm and hand Facial edema became marked about four days before death There was no change in the cardiac observations The liver became progressively enlarged and palpable 8 cm below the costal margin in the midclavicular line, and it was tender Cyanosis, which was of a fairly marked degree, was intermittent During the last few days, as the congestive heart failure became more marked, slight icterus, oliguria, Cheyne-Stokes respirations and stupor supervened, so that the patient died twelve days after admission, presenting a picture of heart failure and uremia

The final clinical diagnosis was cardiac disease ⁹ (a) etiology—unknown active, (b) anatomy—enlarged heart, (c) physiology—sinus rhythm with intra-ventricular block (complete bundle branch) and auriculoventricular block, first stage, (d) functional—class III

Pathologic Report—Necropsy was performed about ten hours after death, the incision being limited to the abdomen. The body was that of an adult white man, weighing 68 Kg, 177 cm in height, well nourished and well developed. Except for moderate pitting edema of the legs, trunk and left arm and slight icterus of the skin and sclerae, external examination gave negative results. On section the panniculus was yellow and of normal thickness, the muscles were pale brown.



Fig 3—The opened heart, showing marked dilatation of the left ventricle and the mural thrombus at the apex. Note the normal mitral and aortic valves.

Examination of the serous cavities showed that the peritoneal cavity contained about 500 cc of clear, straw-colored fluid. Each pleural cavity contained about 300 cc of clear fluid. The pericardial sac contained about 75 cc of clear fluid. Otherwise, the serous sacs were intact.

The heart was large, weighing 600 Gm. Its external measurements were 16 by 13 by 9 cm. It was so soft and flabby as to mushroom over the supporting hand. All of the chambers were markedly dilated. The papillary muscles of both ventricles were flattened. The mitral valve and its chordae tendineae were

⁹ This diagnosis conforms to the nomenclature for cardiac diagnosis recommended by the American Heart Association (Am Heart J 2 202, 1926-1927)

normal. The orifice of the valve measured 10 cm in circumference. The aortic orifice measured 6 cm in circumference; the cusps were normal. The orifice of the tricuspid valve measured 11.5 cm in circumference; the valve and its chordae tendineae were normal. The pulmonary orifice measured 6 cm in circumference; its cusps were normal. The myocardium of the left ventricle measured 18 mm in thickness at the base of the ventricle, 10 mm near the apex and from 2 to 3

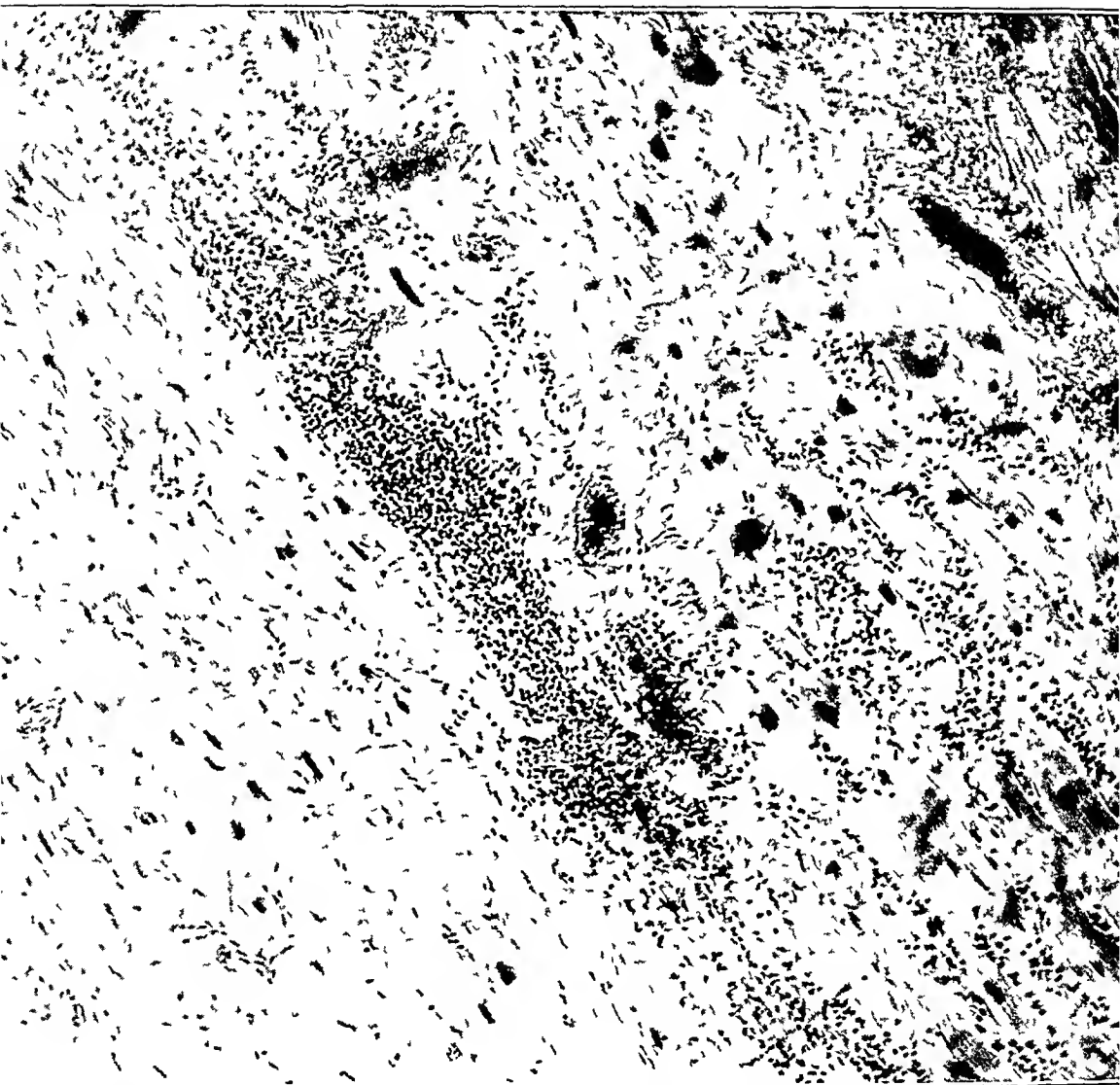


Fig. 4—Low power photomicrograph of a section of the left ventricle. Note the hypertrophied nuclei and muscle fibers, and the diffuse and patchy cellular infiltration by small round cells. Hematoxylin and eosin stain.

mm at the apex. The right ventricle measured 6 mm in thickness at the base and 3 mm at the apex. The epicardium was normal, except for a few pinhead-sized, smooth, glistening points of thickening over the right auricular appendage. The endocardium was intact throughout, except at the apex of the left ventricle, where a firm, grayish-red thrombus was found attached to the endocardium. The right auricular appendage was filled by a similar thrombus. On section, the myo-

cardium, particularly that of the left ventricle, was remarkably altered, brown and brownish-yellow streaks being scattered throughout, nearby were seen irregular bands of gray and grayish-yellow firmer tissue. On section, the linear markings of the muscle bundles were barely visible. The coronary orifices and arteries were normal.

Both lungs were heavier than normal, the pleural surfaces were smooth. The cut surfaces were reddish-blue and oozed frothy sero-sanguineous fluid, they were otherwise normal.

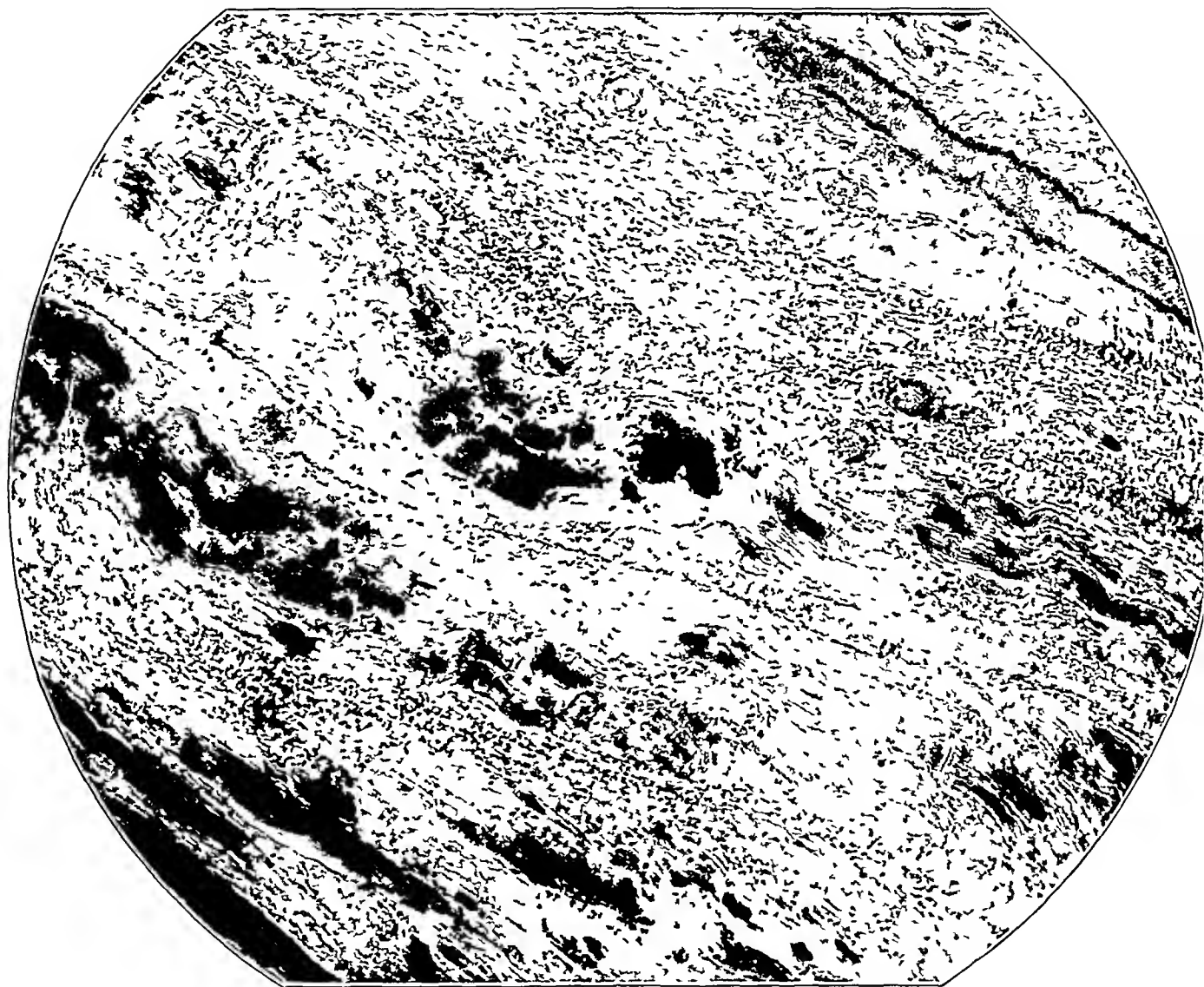


Fig 5—Low power photomicrograph of a section of the left ventricle close to the A-V sulcus posteriorly. Note the replacement of the muscle fibers of the heart by cellular infiltration. Hematoxylin and eosin stain.

The liver weighed 1,300 Gm. The capsule was smooth. The cut surface was firm, showing the markings of chronic passive congestion which gave the organ a nutmeg appearance. The gallbladder and biliary passages were normal.

The spleen was normal in size and shape, weighing 220 Gm. On section, the pulp was firm and red, and the follicles were fairly prominent.

The kidneys were somewhat enlarged, weighing 420 Gm together. The capsules stripped easily, leaving a smooth surface. On section, they were normal, except for slight hyperemia and one small, gray, apparently healed infarct in the right kidney.

The pancreas, suprarenal glands, bladder, prostate and testes appeared normal.

Microscopic Observations—Sections were taken from both ventricles, both auricles, the auricular appendages, valves, papillary muscles, aorta and pulmonary artery of the heart. The following stains were used: hematoxylin-eosin, van

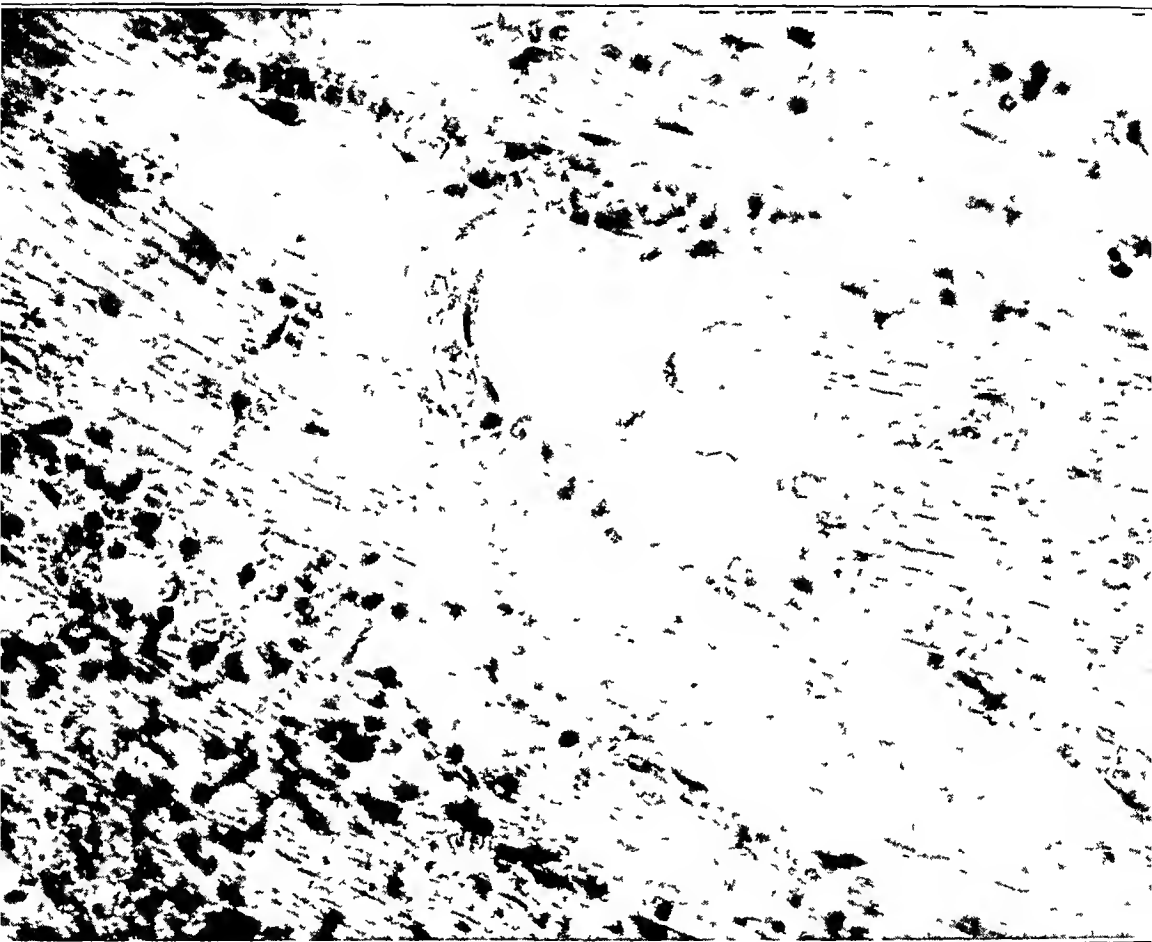


Fig 6—High power photomicrograph of a section of the right ventricle, showing new capillaries traversing the muscle fibers. Note the marked hyperemia. Hematoxylin and eosin stain.

Gieson, Mallory's connective tissue stain, Weigert's elastic tissue stain, sudan III, Nile blue, Gram-Weigert, methyl violet, Unna-Pappenheim, Levaditi and Warthin-Starry.

Sections from various portions of both ventricles revealed marked hypertrophy of the nuclei and fibers of the muscles, both of which were many times larger than in normal circumstances. The interstitial connective tissue was increased in amount. The coronary arteries and arterioles were apparently normal. Newly formed blood vessels were abundant and injected. In places they were seen growing into and between muscle bundles and fibers. No lipochrome pigment was seen.

The lesion noted was widely distributed and more marked in the myocardium of the left ventricle. Areas of considerable dimension were found consisting of degenerated, edematous muscle fibers and nuclei, infiltrated by large numbers of lymphocytes, endothelial cells, fibroblasts and newly formed blood vessels. These areas were irregular in outline and poorly demarcated, and they did not present a constant picture, the several elements varying in number and location. In some places there was an abundance of young connective tissue cells with a few lympho-

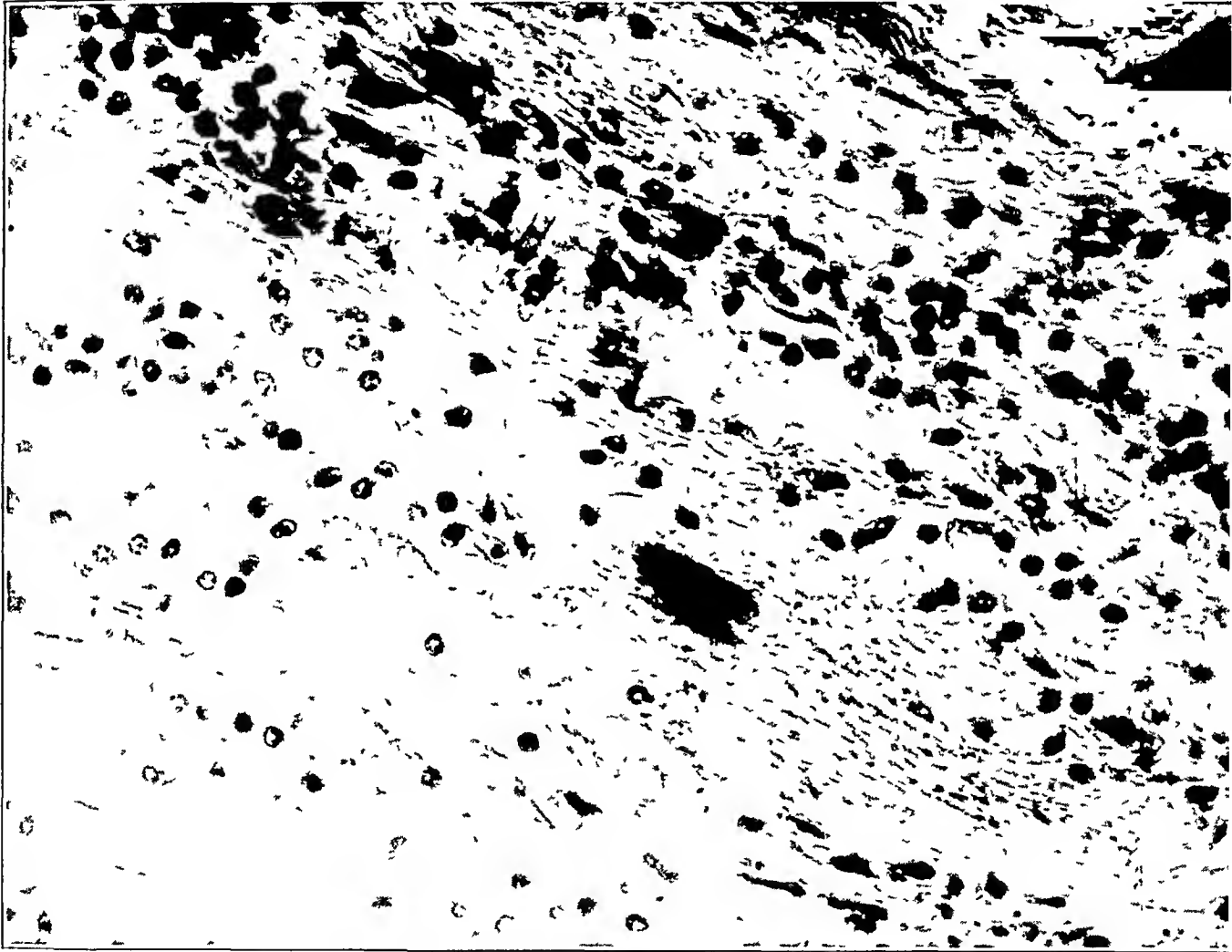


Fig 7—High power photomicrograph of a section of the left ventricle, showing diffuse cellular infiltration, notably of the round cells, occasionally by cells of endothelial type, and replacement of the muscle fibers of the heart. Hematoxylin and eosin stain.

cytes and an occasional plasma cell, in other places focal collections of lymphocytes, a few plasma cells and large endothelial cells were found in and around edematous muscle fibers. Some of the endothelial cells presented sharply outlined nuclei, and in their cytoplasm a fine granular pigment was occasionally seen. No giant cells or Aschoff bodies were found in any of the sections. One small coronary artery was found to contain a small nonoccluding parietal thrombus composed of fibrin, in the meshes of which a few leukocytes could be seen. Near the well marked areas of inflammatory reaction small focal areas of muscle necrosis

were encountered with no surrounding inflammatory reaction. The cross striations of the muscle fibers were normal, except in the areas of degeneration. Fat was not markedly increased in amount, with the sudan III stain it could be seen in fine droplets in most of the myocardial fibers. Sections stained by the van Gieson and Mallory connective tissue methods showed scattered foci of fibrous connective tissue. These were chiefly interstitial. With these stains the interstitial elements

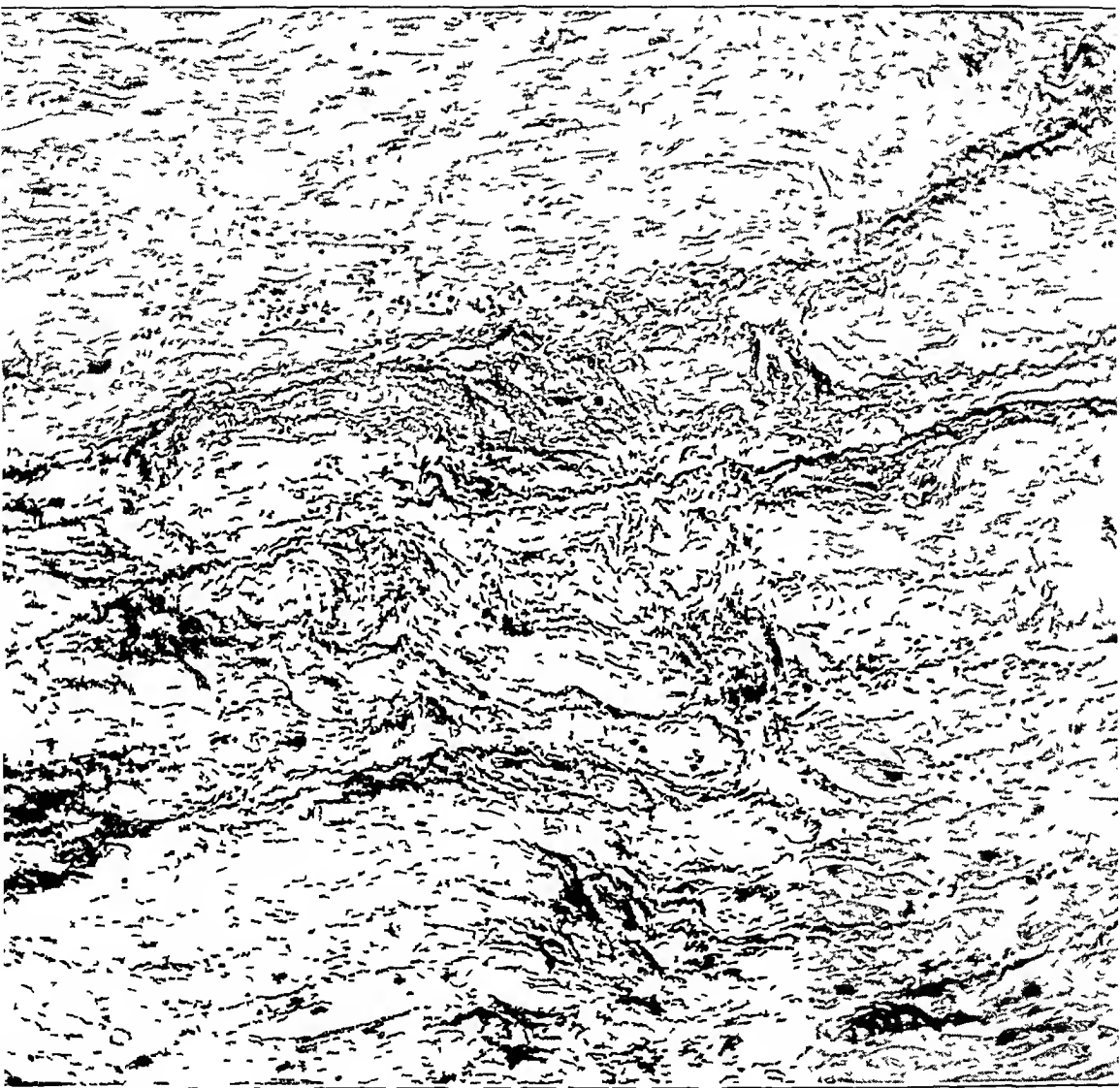


Fig 8—Low power photomicrograph of the myocardium of the left ventricle. Note the diffuse intrafascicular increase of fibrillary connective tissue. Van Gieson stain.

in the areas of degeneration of the muscle were seen as fine fibrillar bands with no intervening stained sarcoplasm. Polymorphonuclear leukocytes and eosinophils were scarce. No areas of hemorrhage were seen.

A section from the apex of the left ventricle revealed a fairly advanced organizing process, involving the endocardial thrombus and the adjacent muscle. Sections of the valves and the endocardium revealed normal structures except at the

apex, as noted. Sections of the aorta and pulmonary artery showed no changes. The stains for amyloid, bacteria and spirochetes yielded negative results.

Sections of the lungs revealed numerous cells indicative of heart failure, occasional areas of edema and marked hyperemia of the small vessels. Sections of patchy atelectasis could be seen.

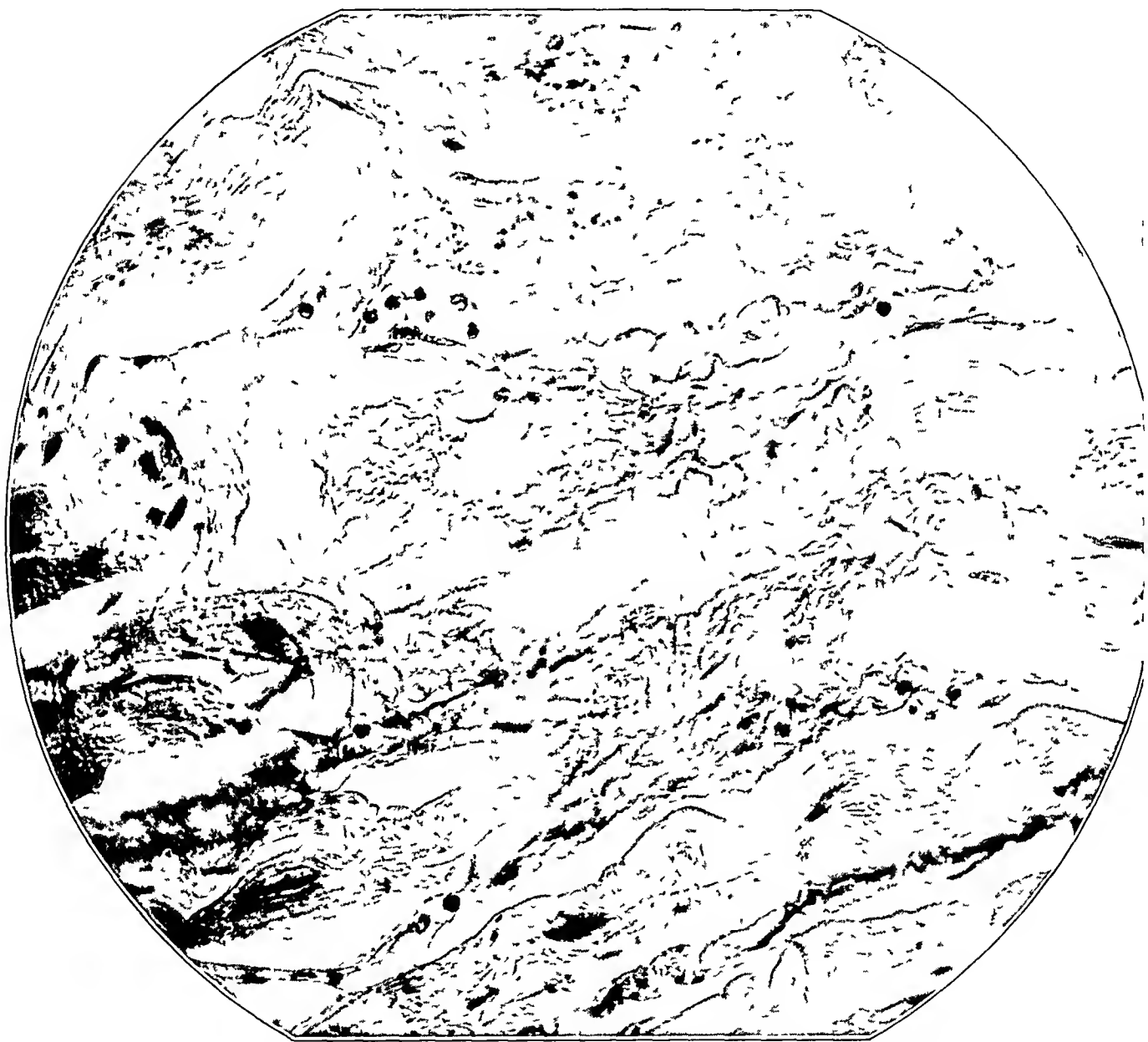


Fig 9—High power photomicrograph of a section of the left ventricle. Note the loose fibrillary connective tissue in an area of necrosis with no cellular reaction. Van Gieson stain.

The central veins of the liver and the adjacent sinusoids were choked with blood elements compressing the cords of the liver. In some of the lobules central necrosis was seen. Considerable bile pigment was seen in the liver cells.

The capsule of the spleen was thin. The splenic sinuses were markedly congested. The follicles were hyperplastic. The arterioles showed no changes.

Most of the glomeruli in the kidneys were normal. An occasional glomerulus was seen with swollen lining cells in Bowman's capsule. The tubules were fairly

well preserved. Many of the proximal convoluted tubules showed marked cloudy swelling. The lumina contained epithelial and hyaline casts. Section through the area of infarction revealed replacement of the parenchyma by dense acellular connective tissue. The edges were sharply defined.

The pathologic diagnosis was subacute productive myocarditis, hypertrophy and dilatation of the heart, mural thrombus of the left ventricle and the right

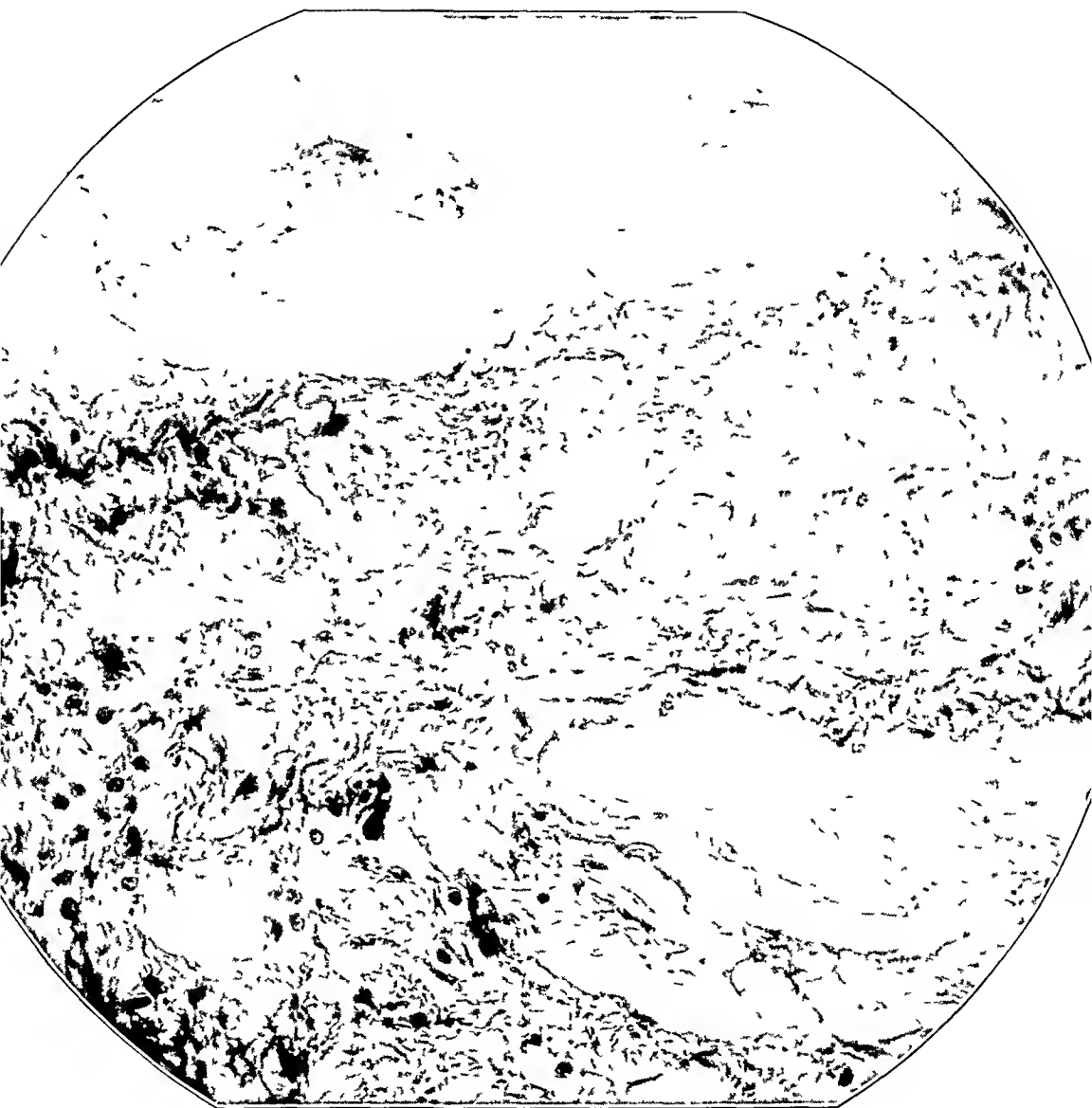


Fig 10—High power photomicrograph of the myocardium of the left ventricle. Note the increase in connective tissue which is more dense than in figure 9, extending between and replacing muscle bundles, note, too, the moderate round cell infiltration. Van Gieson stain.

auricular appendage, healed infarct of the right kidney, chronic passive hyperemia of the lungs, liver, spleen and kidneys, follicular hyperplasia of the spleen, cloudy swelling of the kidneys, generalized edema, ascites and icterus.

COMMENT

Progressive heart failure was the outstanding clinical feature in our case. This is in accord with the observations of previous authors.

Careful search of the history in this case for an etiologic factor was unavailing. There was no history of any of the well known infectious diseases, including rheumatic fever, diphtheria, scarlet fever, syphilis or tuberculosis, nor were we able by any means available to demonstrate an etiologic agent. Two blood cultures taken during the patient's stay in the hospital were sterile.

The exact onset of the disease in this case is doubtful. The embolic phenomena noted during life and the evidence for the same found at necropsy are particularly noteworthy and possibly give a clue to the onset and duration of the lesion.

In 1901, Josserand and Gallavardin¹⁰ recorded three cases of Fiedler's myocarditis with careful clinical and pathologic studies. These cases occurred in young men in the third decade. In each case, they emphasized the abrupt onset with embolic manifestations, pulmonary or cerebral, followed by progressive myocardial failure.

In our case, the cerebral accident about eight and one-half months before death, the healed infarct in the kidney and the probable pulmonary infarct about six weeks before death suggest that the intracardiac thrombi were present for some time. During the patient's first hospitalization, it was noted further that the heart was enlarged, the apex being 1 cm. to the left of the midclavicular line in the fifth interspace. Moreover, the heart weighed 600 Gm. and exhibited marked hypertrophy, lending further support to the contention that the disease had existed for a period of months.

Of considerable clinical interest are the data obtained by electrocardiography, which gave further evidence of the extensive distribution of the lesion, i. e., first stage auriculoventricular block (P-R interval from 0.20 to 0.24) and complete intraventricular block.

The gross and microscopic observations demonstrate the distribution of the lesion. The diffuse and focal cellular infiltration consisting chiefly of lymphocytes, the new formation of blood vessels and connective tissue, involving both the interstitium and the parenchyma, the well marked deposits of organized connective tissue and the focal areas of necrosis account for the progressive circulatory failure. Careful microscopic studies have not been made of the conducting tissue. There were no vascular, perivascular or myocardial lesions suggesting rheumatic infection, and no Aschoff bodies were found.

10 Josserand, E., and Gallavardin, L. De l'asystolie progressive des jeunes sujets par myocarditis subaigue primitive, *Arch. gen. de med.* **78**: 513 and 684, 1901.

The necropsy observations adequately account for the clinical course. The etiology in our case remains obscure. Whether or not the lesion was an atypical rheumatic inflammatory reaction cannot be answered. Aschoff⁸ felt that the lesions in his case could not be explained or described as rheumatic alone. He suggested that some other etiologic factor was combined or superimposed, possibly an infection of cryptogenic origin. We believe, with Scott and Saphir, that to regard these cases as rheumatic would not aid in clarifying the knowledge of their pathogenesis.

SUMMARY

A case of so-called isolated myocarditis of unknown etiology is reported.

The clinical and necropsy observations are compared with those in previously recorded cases.

Electrocardiograms showing evidence of severe impairment of conduction are noted for the first time in connection with this disease.

IV CORONARY SINUS RHYTHM

RHYTHM SUBSEQUENT TO DESTRUCTION BY RADON OF THE SINO-AURICULAR NODES IN DOGS *

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It has usually been assumed that when the sino-auricular nodes in the hearts of dogs have been completely destroyed the auriculoventricular node, particularly its coronary sinus portion, becomes the pacemaker or the initiatory mechanism. Eyster and Meek¹ reported in such cases a decreased p-r interval and a decreased cardiac rate. Borman,² however, obtained normal electrocardiograms from dogs in which the sino-auricular nodes had been destroyed by radon. Therefore, it was our primary object in this study to determine the exact site of the initiation of the impulse in a larger series of dogs in which complete destruction of the sino-auricular nodes was similarly produced by radon.

METHOD

In a series of thirty dogs, the sino-auricular nodes were aseptically exposed. The only modification of the previously described technic² consisted in the use of capillary tubes containing radon which were either inserted subepicardially by means of a right angle applicator, or as in the later experiments, by tying the radon seed with silk sutures to the epicardium overlying the sino-auricular node. By careful asepsis, a subcuticular closing suture being used, practically primary closure of the wound of the chest was obtained. The duration of the operation varied from twenty to forty minutes. After an interval of several weeks or months, during which electrocardiograms were taken, the animals were again anesthetized, tracheotomy performed, the internal mammary vessels ligated and the sternum and portion of the attached ribs resected, exposing the pericardial sac. The latter was incised and the margins sewed to the edges of the wound. Auricular systole was recorded on the electrocardiographic record by means of the transmission of air and a recording tambour. Fine silk sutures were inserted over the head of the sino-auricular node and the body of the right atrium, catching only a tiny portion of the epicardium. By means of the long ends of these sutures, a woollen

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1 Eyster, J A E, and Meek, Walter J. The Permanent Rhythm Following Destruction of the Sino-Auricular Node, *Am J Physiol* **61** 117, 1922

2 Borman, Milton C. Destruction of the Sino-Auricular Node in Dogs' Hearts by Radon, *Am Heart J* **3** 208, 1927

strand moistened in physiologic solution of sodium chloride was tied to each suture. The ends of the sutures and woolen strands were neatly and closely cut, so that contact with the epicardial surface was obtained at a very small point. Each of the woolen strands passed upward into a glass tube, the lower end of which was packed lightly but firmly enough to avoid leakage with the wool soaked in physiologic solution of sodium chloride. The remaining portion of the glass tube was filled with a saturated solution of zinc sulphate. The leads of an electrocardiograph were connected to the electrodes by a small zinc rod freshly cleansed with sulphuric acid, and dipped in mercury. By changing these zinc rods, which were dipped in the upper end of the glass tubes containing the solution of zinc sulphate, leads could be quickly interchanged, furnishing a check in the determinations of negativity. If the initial deflection was an upstroke when the

TABLE 1—*Electrocardiograms Before and After Operation on Dog 8*

No	Condition	p r Interval in Seconds	Cardiac Rate	Abnormalities
1	Normal	0 11 0 12	90	
2	47 minutes after administration of 1 grain of morphine sulphate subcutaneously	0 11 0 12	100	
3	53 minutes after administration of morphine sulphate and 4 minutes after injection of 0.001 Gm of atropine sulphate	0 12 0 14	120	
4	10 hours after 2.09 millicuries of radon implanted	0 09 0 11	75	
5	23 hours after operation	0 09 0 10	60	
6	33 hours after operation	0 08 0 10	84	p waves barely visible
7	2 days after operation	0 10 0 11	100	
8	3 days after operation	0 10 0 12	108	
9	5 days after operation	0 11 0 13	70	Cycles of sino auricular block
10	6 days after operation	0 13 0 14	60	Cycles of sino auricular block
11	9 days after operation	0 10 0 12	100	Cycles of sino auricular block negative T ² and T ³
12	17 days after operation	0 11 0 12	100	T in all leads negative
13	23 days after operation	0 10 0 12	100	T in all leads negative
14	33 days after operation	0 10 0 12	100	T in all leads negative
15	120 days after operation	0 10 0 12	100	Just prior to experiments on initial negativity
16	Body of right auricle initially negative when compared to sino auricular node			
17	Coronary sinus initially negative when compared to sino auricular node			
18	The same with leads inverted			
19	Body of right auricle negative when compared to sino auricular node			
20	Coronary sinus initially negative when compared to body of right atrium			
21	The same with leads inverted			
22	Coronary sinus initially negative when compared to auriculoventricular node			
23	The same with leads inverted			
24	Auriculoventricular node initially negative when compared to sino auricular node			
25	Normal electrocardiogram with indirect Einthoven leads p r interval 0 12 cardiac rate 130			

lead of the right wrist was over the sino-auricular node, the latter must be regarded as initially negative when compared to any other point. A glass rod curved almost at right angles, the lower end of which was packed with wool soaked in physiologic solution of sodium chloride, was placed behind the heart over the region of the coronary sinus. A fourth electrode, a slightly curved glass rod, was passed down the external jugular vein into the right side of the heart, the end was rotated medially so that it touched the base of the interauricular septum in the region of the auriculo-ventricular node. Thus at the termination of each experiment, the point of origin of the cardiac impulse was determined. Thereafter, the sino-auricular junctional tissues were fixed in formaldehyde, drawings were made of the gross anatomic changes, and the tissues were mounted in paraffin blocks. Duplicate sets of semiserial sections of each block were made and stained with hematoxylin and van Gieson's stains. Sections were stained from every 1 to 3 mm of tissue.

DATA

Two series of animals were used in these experiments. In the 1927-1928 series, nine animals were used while in the 1928-1929 series

TABLE 2—*Summary Data on All Animals*

No	Days of Radon Lived in Tube	Milliecurie	Postoperative Changes in Electrocardiogram	Seat of Initiation of Impulse	Anatomic Observations
1927-1928 Series					
5	120	0.99	p r interval before operation, 0.14-0.14 second, thirty-ninth day after operation, 0.12-0.13 second, cycles of sino auricular block, inverted T ² and T ³	Sino auricular node	Pericarditis, acute; no sino auricular node seen
6	120	0.99	p r interval before operation, 0.12 second, forty-fifth day after operation, 0.12-0.14 second	Coronary sinus	Grossly, nodular white scar on endocardial surface at head of node, histologically, necrosis and calcification, no sino auricular node seen
8	120	2.69	p r interval before operation, 0.11-0.12 second, thirty-eighth day after operation, 0.10-0.12 second, cycles of sino auricular block	Coronary sinus	Grossly, round infiltrating scar at head of sino auricular node, histologically, fatty change and hemorrhage, no sino auricular node seen
1928-1929 Series					
5	41	4.00	p r interval before operation, 0.13-0.14 second, thirty-seventh day after operation, 0.11-0.12 second, on seventh day after operation, delayed conduction, seven cycles of nodal rhythm	Coronary sinus	Grossly, epicardial adhesions, hemorrhagic changes from sino auricular junction caudally for 3 cm, 15 mm in width, histologically, free hemorrhage, replacement of connective tissue, infiltration of round cells, no sino auricular node seen
9	30	3.50	Before operation, inverted T-, p r interval, 0.12-0.15 second, twenty-sixth day after operation, inverted T-, p r interval, 0.14-0.16 second, decreased vagal tone, series of nodal cycles	Coronary sinus	Grossly, marked thickening 1 cm above junction on both vena cava and on auricular side, and down 3 cm below the junction, histologically, similar to changes in dog 5
13	20	4.30	Before operation, p r interval, 0.14-0.15 second, fifteenth day after operation, p r interval, 0.175-0.24 second, occasional sino auricular block	Head of sino auricular node	Grossly, white scar 15 mm in length, 7 mm in width, over the crista terminalis endocardially, considerable hemorrhage, histologically, nutrient artery visible, surrounded by extensive coagulative necrosis and hemorrhage, no sino auricular node seen
19	21	8.00	Before operation, p r interval, 0.135-0.165 second, twentieth day after operation, p r interval 0.09-0.11 second, on second day after operation, almost complete nodal rhythm on fourth day, auriculo ventricular block	Sino auricular node	Grossly, white scar 2 cm long and 6 mm wide over crista, surrounded by area of hemorrhage, also visible endocardially, histologically, coagulative necrosis with hemorrhage in crista terminalis, no sino auricular node seen

twenty-one animals were studied. In both series, preoperative and postoperative records showing the effects of morphine and atropine were obtained, which data may form the substance of a further report. The first three reports in table 2 were from the 1927-1928 series. The last four animals were from the later series. From the total group

the data of only seven were included in table 2, because only in these were both initial negativity and histologic observations made. While histologic examinations were made in each experiment, many of the animals died from various causes or during the determination of initial negativity.

The following protocol of dog 8 illustrates the method used.

Dog 8 was operated on the day after a normal electrocardiographic study had been made, including tracings after the hypodermic administration of morphine and atropine. An implant containing 2.09 millicuries of radon was introduced beneath the epicardium overlying the sino-auricular node. At intervals during the following four months, electrocardiograms were obtained. The animal was prepared for direct electrocardiographic tracings in the manner previously described, and the point of initial negativity was noted by comparing the sino-auricular node to the body of the right auricle, the auriculoventricular node and the region of the coronary sinus, and vice versa. Examination of the junctional tissues revealed a large scar replacing all the tissue at the head of the crista terminalis. Histologically, no sino-auricular nodal tissue was seen. The tissue comprising the crista terminalis was replaced by scar, free hemorrhage and extensive fatty change.

Table 1 summarizes the electrocardiographic studies performed on dog 8. The combined data on all animals are summarized in table 2.

COMMENT

The use of radon (radium emanation) was first suggested to one of us by Dr. J. E. Sweet of Cornell Medical School several years ago when we were interested in a new method of destroying the sino-auricular node in the hearts² of dogs. In two of the animals studied at that time, cycles of nodal rhythm or ventricular escape were noted. Histologically, we were unable to find any evidence of sino-auricular nodal tissue in these two animals although no such difficulty was experienced in others. It was therefore a natural assumption that a coronary sinus rhythm had probably developed in these two animals, although the electrocardiograms did not show a reduction in the p-r intervals or a decreased cardiac rate. The experiments conducted since that first report differed from the former ones in that larger doses of radon were used and that at the termination of the long-time experiments Lewis' method of determining initial negativity was used to find the origin of the cardiac impulse.

In dog 5 (series of 1927-1928), cycles of sino-auricular block with inverted T² and T³ waves were noted several months after the application of 0.99 millicuries of radon over the sino-auricular node. Although it was finally determined that the seat of the initiation of the impulse was in the sino-auricular node, histologically no sino-auricular structure was found. This was probably due to faulty histologic technic, the sections being poorly cut and stained.

Fig 1 (dog 3)—This dog was not included in the data because the animal died on the table during operation before determinations of the initial negativity could be completed. Preoperative record after the animal had received $\frac{1}{2}$ gram of morphine sulphate subcutaneously. Result: normal rate and rhythm.

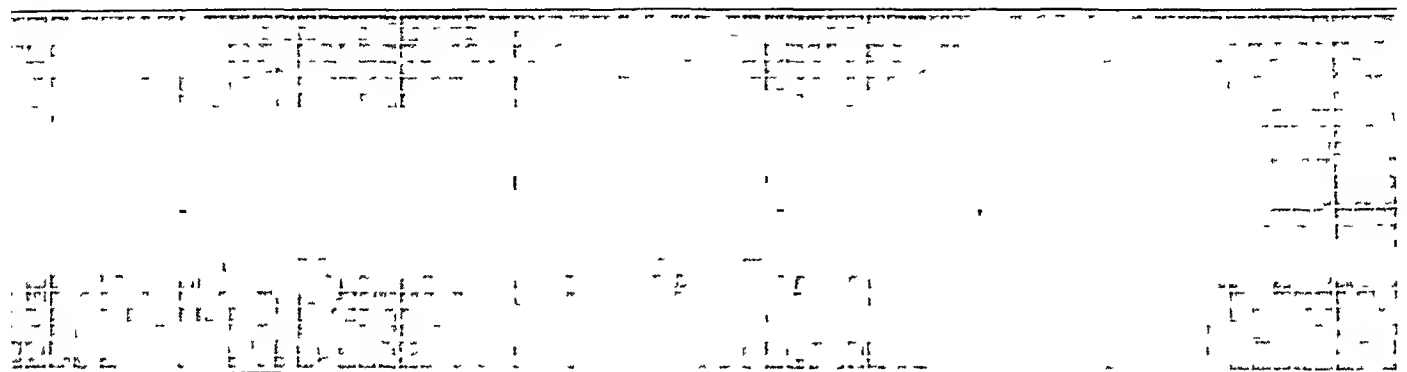


Fig 2 (dog 3)—Postoperative record 119 days after constant exposure of the sino-auricular node to 0.1 millicuries of radon, immediately afterward $\frac{1}{2}$ gram of morphine sulphate was injected subcutaneously. Result: occasional cycle of sino-auricular block with decreased rate.

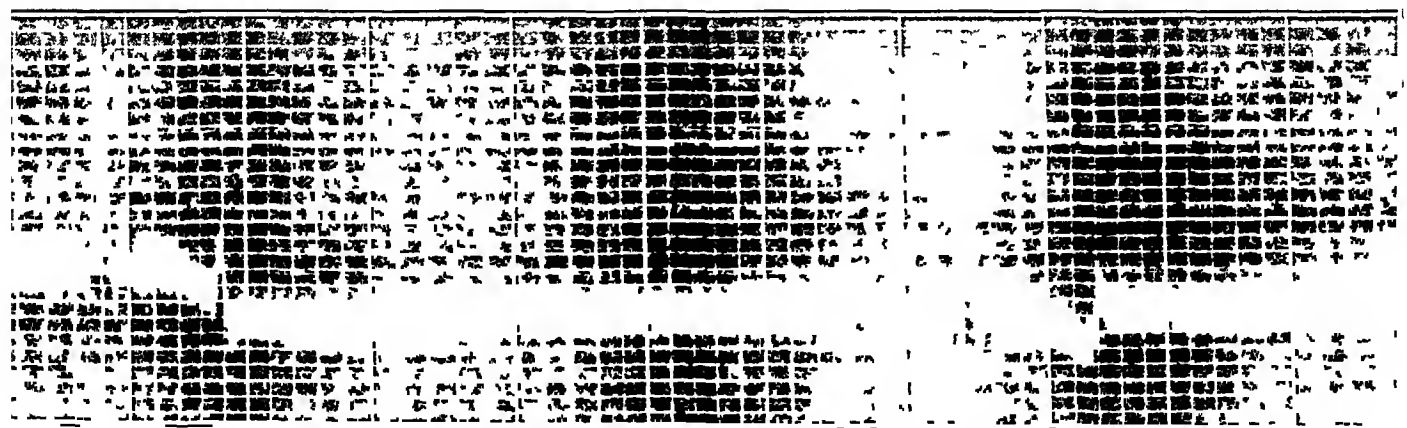


Fig 3 (dog 5)—Occasional cycle of sino-auricular block four days after the introduction of 0.99 millicurie of radon over the sino-auricular node.

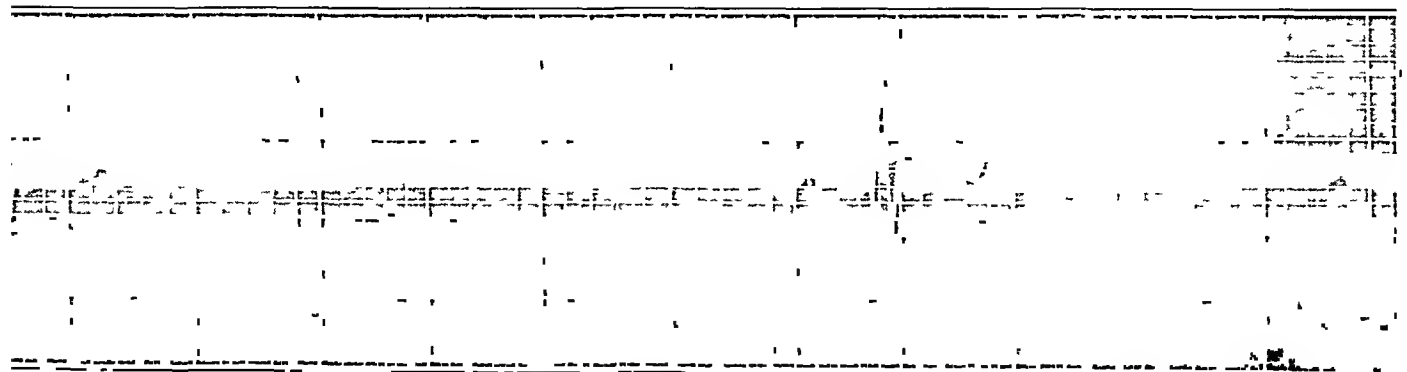


Fig 4 (dog 6)—Occasional cycle of sino-auricular block ten days after constant exposure of the sino-auricular node to 0.99 millicurie of radon.

In Dog 6 (series of 1927-1928), no noteworthy electrocardiographic changes were observed. Histologically, no nodal tissue was found, and the site of the initiation of impulse was found to be at the coronary sinus. In this experiment there was definite evidence of coronary sinus rhythm with a p-r interval of from 0.12 to 0.14 second and a heart rate of 70, compared with a normal preoperative p-r interval of 0.12 second and a cardiac rate of 80. Under the conditions of this experiment, although two and one-half days after operation there was a shortening of the p-r interval by 0.02 second at the time the method of determining initial negativity was used, 120 days later, the p-r interval was again normal.

In dog 8 (series 1927-1928), on the thirty-eighth day after operation, the cardiac rate and p-r intervals were relatively unchanged, the pulse was found to arise in the region of the coronary sinus, and histologically there was no sino-auricular tissue. Cycles of sino-auricular block were observed during the second week after operation.

In dog 5 (series 1928-1929), in which 4 millicuries of radon was used, more marked changes of rhythm were found. One week after operation, delayed conduction and as many as seven consecutive cycles of nodal rhythm at the rate of 37.5 per minute interspersed between normal cycles and occasional right ventricular premature beats were found. In this animal no sino-auricular tissue was found histologically, and the impulse was found to arise from the coronary sinus. The normal preoperative p-r interval was from 0.13 to 0.14 second and the cardiac rate 90, and thirty-seven days after operation, in the presence of what seemed electrocardiographically to be a normal rhythm, the p-r interval was from 0.11 to 0.12 second and the cardiac rate only 39. This bradycardia seems significant in that it further suggests the initiation of the impulse in the coronary sinus.

In dog 9 (series 1928-1929), after operation, a series of cycles of nodal rhythm was noted together with evidence of decreased cardiac vagal tone. Before operation the p-r interval was from 0.12 to 0.15 second, and after operation it had increased until it was from 0.14 to 0.17 second. Before and after operation there was an inverted T² wave, and during the introduction of the tube of radon this animal was the only one in which an auricular fibrillation was produced. Terminally, the coronary sinus was found initially negative, and histologically no nodal tissue was found.

In dog 13 (series 1928-1929), the sino-auricular node was initially negative, and histologically the crista terminalis showed a visible nutrient artery with extensive coagulation necrosis and hemorrhage into the surrounding tissue. It was inconceivable that such tissue could function. In this animal occasional cycles of sino-auricular block were observed, but no other electrocardiographic changes were noted.

In dog 19 (series 1928-1929) histologically there was a similar destruction of tissue at the site of the sino-auricular node while the impulse originated terminally in the sino-auricular nodal area. On the twelfth day after the introduction of radon, the animal was in almost

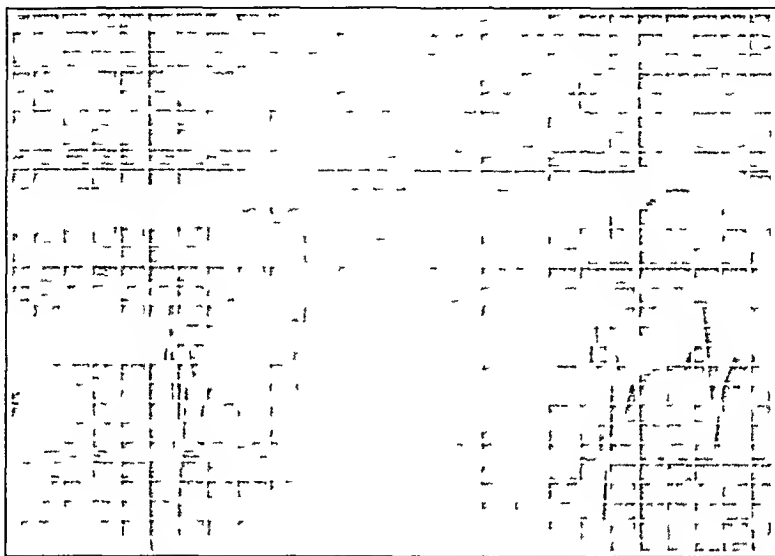


Fig 5—The right electrode on the sino-auricular node, the left, on the body of the right auricle. Result auricle initially negative (Figures 5, 6, 7 and 8 represent experiments on initial negativity in dog 6, in each record the upper wave indicates auricular contractions, the lower wave, simultaneous direct electrocardiograms)

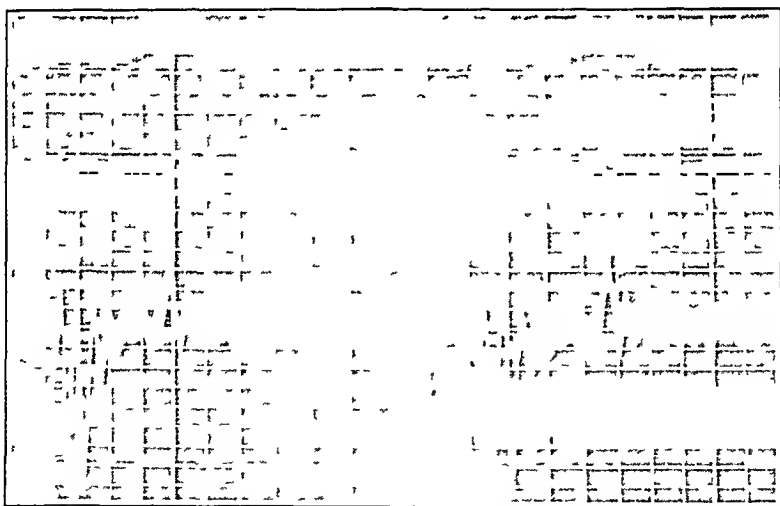


Fig 6—The right electrode was on the sino-auricular node, the left, on the coronary sinus. Result coronary sinus initially negative

complete nodal rhythm. At the end of the experiment, prior to the determination of the initial negativity, only an occasional nodal cycle was observed, and the p-r interval had been reduced to from 0.09 to 0.11 second from a normal preoperative p-r interval of from 0.135 to 0.165 second.

In three of the seven animals the sino-auricular node proved to be initially negative, but the gross and histologic changes in this region were so extensive as to render it unlikely that the sino-auricular node could function. For this we offer no certain explanation. It is barely possible that the immediate surrounding tissue initiated the cardiac impulse or that small outlying remnants of the sino-auricular node escaped destruction and initiated the impulse. In each of the seven experiments the point of initial negativity remained unchanged throughout that single experiment when compared with all outlying points. If the electrodes were changed, the observations were the same. Therefore, we place greater reliance on the observations of initial negativity than on the negative histologic observations.

In no experiment have we been able to obtain a permanent auriculo-ventricular nodal rhythm. This corroborates the observations of others and ourselves. We attribute the shorter period of nodal rhythm in our experiments as compared with other experiments in which the sino-auricular node had been ligated and excised to the more gradual process of destruction in the experiments with radon. This fact indicates the greater reliability of the method using radon, and also verifies previous observations in the more acute experiments.

The finding of cycles of auriculoventricular block in these experiments suggests that although the impulses continued to arise from the sino-auricular node directly beneath the implant of radon, changes were brought about that interfered with the transmission of the impulse through the auriculoventricular node. More frequently, however, cycles of sino-auricular block were noted which suggested that there was interference with the impulse originating in the sino-auricular node during its transmission to the auriculoventricular node.

In several instances it was observed that following the hypodermic administration of $\frac{1}{2}$ grain (0.0324 Gm.) of morphine sulphate, nodal rhythm followed in animals showing postoperative changes in rhythm such as sino-auricular block and cycles of nodal rhythm. This suggests that the early stimulating vagal effect of morphine is more effective in inhibiting the functioning of the coronary sinus than that of the normal sino-auricular node. Therefore, in the normal dog, it is possible that if the administration of morphine produces a nodal rhythm it might be inferred that the animal had a coronary sinus rhythm prior to the injection of the drug, or that the vagal tone was excessively great. This point, however, needs further verification.

No matter what the actual process underlying the electrocardiogram may prove to be, whether it is produced by the passage of the impulse along specialized tissue or whether it is due to chemical changes or to actual muscular contraction, there can be no doubt that the shape and time relation of the waves secured by the usual leads depends on the

order in which the excitation sweeps over the heart. The real problem in our experiments is to account for the normal electrocardiograms when the sino-auricular node is destroyed, when the pacemaker must be in a lower part of the specialized tissue and when excitation must be

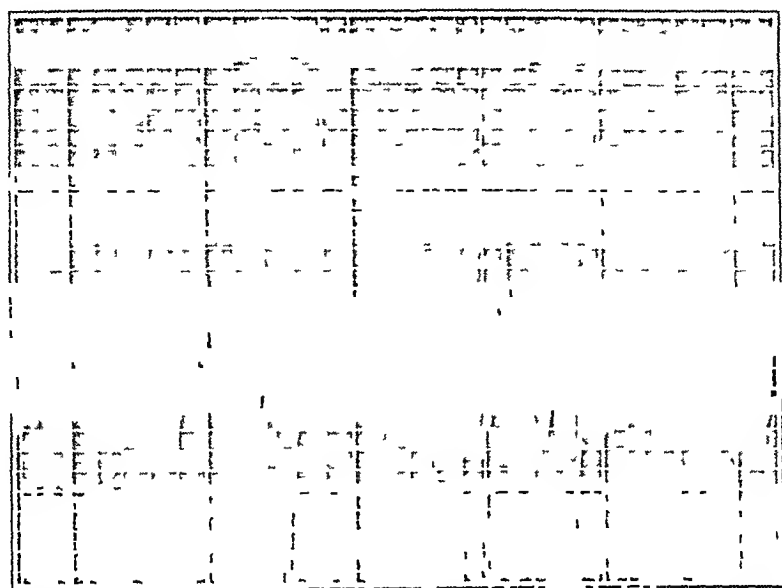


Fig 7—The right electrode was on the coronary sinus, the left, on the body of the right auricle. Result: coronary sinus initially negative.

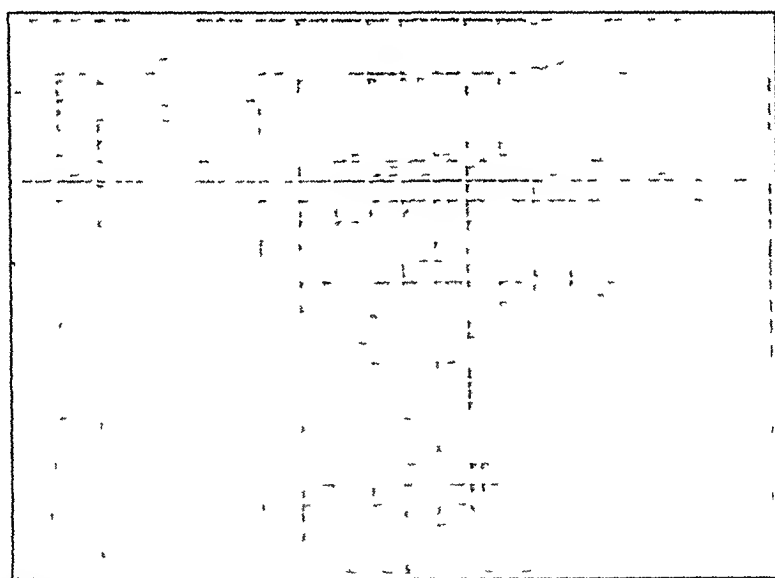


Fig 8—The right electrode was on the auriculoventricular node, the left, on the coronary sinus. Result: coronary sinus initially negative.

delivered to the myocardium at other than the usual place. If excitation were instantaneously transmitted as Mackenzie³ believed there might

³ Mackenzie, James. *Diseases of the Heart*, London, H. Frowde, Hodder & Stoughton, 1923, p. 424.

be a way out of our difficulties, but this idea is not tenable in the light of present information. The question is: How can the coronary sinus, the undoubted seat of initial negativity in some of our experiments, deliver a stimulus to the auricle so that the p wave is normal in all of its characteristics and the p-r interval of the usual value? At present, we have no answer to the question that is based on experimental evidence. It may be that the impulse from the coronary sinus reached the auricle over a pathway to the region of the sinus and thus was finally distributed in the usual manner. Although it is difficult to understand how this could take place in view of the extensive and advanced destruction of the sino-auricular nodal tissue, it is more difficult to see that there should be no reduction in the p-r interval.

Eight years ago, Eyster and one of us¹ noted a decrease in the p-r interval of 0.03 second and about a 25 per cent decrease in the average cardiac rate in coronary sinus rhythm in dogs in which the sino-auricular nodes had been ligated and excised. It is possible that

TABLE 3—*Data of a Previous Series of Fourteen Dogs*

Dog	Preoperative		Days After Operation	Postoperative	
	p-r Interval	Cardiac Rate		p-r Interval	Cardiac Rate
2	0.09 0.12	100	81	0.08 0.10	70
			185	0.10 0.11	120
7	0.12 0.13	120	14	0.08 0.10	120
			22	0.12 0.13	130
10	0.09 0.10	100	9	0.06 0.08	70
			137	0.09 0.10	110

in the experiments in which destruction is sudden, certain factors obtain which are not present in experiments in which that destruction is slow, as when it is produced by radon. We have no other explanation to offer for the fact that in the experiments reported herein the p-r interval and the cardiac rate remained normal. It is noted that the period of observation after the destruction of the sino-auricular nodes in the present series is over a much longer period of time than in the series reported by Eyster and Meek. In a personal conversation, Dr Pierre Ryland of Belgium stated that he had noted many examples of coronary sinus rhythm. He expressed the belief that interference with the supply of blood in the sino-auricular region allowed the auriculo-ventricular node to gain a temporary ascendancy over the region of the coronary sinus.

An examination of the data in a previous series of fourteen dogs in which the sino-auricular node was destroyed by radon² revealed the results recorded in table 3.

While these animals (dogs 2, 7 and 10) showed decreased p-r intervals and cardiac rates after operation, after the lapse of a certain

interval of time normal figures for these values were obtained in some animals normal rates were found for an extended period. In dog 2, on the eighty-first day after operation there was still evidence of what might be interpreted as coronary sinus rhythm. In these three animals careful histologic examination revealed the absence of sino-auricular tissue and the replacement thereof with scar tissue and extensive degenerative changes. This observation suggests that possibly if the animals concerning which Eyster and one of us (W. J. M.) reported had been observed over a longer period, a return to normal figures might have occurred.

CONCLUSIONS

- 1 The previous observation that the nodal tissue of the coronary sinus apparently acts as a reserve mechanism, as a pacemaker under conditions of experimental destruction of the sino-auricular node, is corroborated.

- 2 Evidence is presented that suggests that a coronary sinus rhythm cannot be differentiated from a sino-auricular rhythm by means of an electrocardiogram.

- 3 If the sino-auricular node is destroyed gradually by radon, the nodal tissue of the coronary sinus assumes the function of pacemaker.

- 4 It is probable that when the sino-auricular node is rendered functionless by disease the nodal tissue of the coronary sinus acts as pacemaker.

- 5 Permanent nodal rhythm, i. e., a rhythm with a definite and permanently shortened p-r interval, cannot be produced by destroying the sino-auricular node with radon.

- 6 Nodal rhythm temporarily follows the injection of morphine in dogs in which the sino-auricular nodes have been destroyed by radon.

- 7 The electrocardiographic changes in dogs following the destruction of the sino-auricular nodes by radon are temporary reduction of the p-r interval, which later becomes normal, slightly greater or slightly less than normal, decreased cardiac vagal tone, partial and complete sino-auricular block, partial and complete auriculoventricular block, nodal rhythm, coronary sinus rhythm, inverted T² and T³ and premature ventricular beats.

THE APPEARANCE OF HISTIOCYTES IN THE PERIPHERAL BLOOD¹

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REVIEW OF THE LITERATURE

Although the histiocyte is occasionally seen in the peripheral blood, it is usually unrecognized, chiefly, it seems, because the existence of the cell in the circulation is not generally known. Therefore, it was felt that a review of the subject of the histiocyte and of its appearance in various clinical conditions might arouse more general interest in the appearance of the cell and its clinical significance.

The name "histiocyte" signifies literally "tissue cell." It was first used in this connection by Aschoff¹ and Kiyono in 1913, and has come into use as the generic name for the cells of the reticulo-endothelial system. The word histiocyte has many synonyms. It is the macrophage of Metchnikoff² and of Evans,³ the clasmatoocyte of Ranvier⁴ and of Sabin and Doan,⁵ the adventitial cell of Marchand,⁶ the pyriole-blue cell of Goldmann,⁷ the hemohistioblast of Ferrata,⁸ the Ferrata cell of various Italian hematologists,⁹ the monoblast of Merklen and Wolf,¹⁰

¹ Submitted for publication, Oct 10, 1930.

² From the Medical Service and Department of Pathology, Beth Israel Hospital.

1 Aschoff, L. Ein Beitrag zur Lehre von den Makrophagen auf Grund von Untersuchungen des Herrn Dr. Kiyono, Verhandl. d. deutsch. path. Gesellsch. **16** 107, 1913.

2 Metchnikoff, E. Leçons sur la pathologie comparée de l'inflammation, Paris, Masson & Cie, 1892.

3 Evans, H. M. The Macrophages of Mammals, Am. J. Physiol. **37** 243, 1915.

4 Ranvier, L. Des clasmatoocytes, Arch. d'anat. micr. **3** 123, 1899.

5 Sabin, F. R., and Doan, C. A. The Presence of Desquamated Endothelial Cells, the So-Called Clasmatoocytes, in Normal Mammalian Blood, J. Exper. Med. **43** 823, 1926.

6 Marchand, F. Ueber die bei Entzündungen in der Peritonealhöhle auftretenden Zellformen, Verhandl. d. deutsch. path. Gesellsch. **1** 63, 1898.

7 Goldmann, E. E. Die äussere und innere Sekretion des gesunden und kranken Organismus im Lichte der "vitalen Färbung," Beitr. z. klin. Chir. **64** 192, 1909.

8 Franco, E., and Ferrata, A. Cellule istiodi (emoistioblasti) e loro derivati nel sangue circolante, Arch. per le sc. med. **42** 109, 1919.

9 Reitano, D. Emoistioblasti e loro derivati nella leucemia monocitica, Haematologica **3** 524, 1922.

10 Merklen, M., and Wolf, M. Leucemies a monocytes, Rev. de med. **45** 154, 1928.

the "Stammzell" of certain German authors¹¹ and the resting-wandering cell of Maximow¹². The last author, writing in 1927,¹ said that although the word histiocyte was more or less meaningless at least it had world wide acceptance, and therefore its use was probably preferable to that of his own term "resting-wandering cell".

The histiocyte, a large cell containing phagocytosed material was first described as occurring in the peripheral blood by Eichhorst¹⁴ in 1874. This author described fairly numerous cells from four to six times the size of red blood cells in a case of typhoid fever, they contained from two to seven inclusions of red blood cells. The formation of pseudopods was noted in several cells, a few of which contained vacuoles. Eichhorst thought that these cells were probably derived from the spleen, although he considered derivation from a coincident phlebitis possible. Eichhorst cited Remak (1845), who discovered large cells with inclusions of red cells occurring in the splenic pulp of calves, horses and dogs after venesection, and Gulliver (1842), who found from one to six red blood cells in certain "lymphocytes" in a horse dying of phlebitis. In 1907, Rowley¹⁵ found the phagocytic "lymphocyte" in the blood from patients with tertian malaria and lymphatic leukemia, and in 1908 she described¹⁶ a case of "fatal anemia associated with enormous numbers of circulating phagocytes". The blood from this patient was studied in a warm chamber as well as with fixed preparations. Appended to this article are a large number of excellent photomicrographs showing the process of phagocytosis¹⁷. In 1907 Van Nuys¹⁸ and in 1911, Leede¹⁹ first found phagocytic cells in subacute

11 Ewald, Frehse and Hennig. Akute Monozyten—und Stammzellen—Leukämien, *Deutsches Arch f klin Med* **138** 353 (Feb) 1922

12 Maximow, A. Untersuchungen über Blut und Bindegewebe, *Arch f mikr Anat* **73** 444, 1909

13 Maximow, A. Les relations des cellules sanguines avec le tissu conjonctif et avec l'endothélium, *Ann anat path* **4** 701, 1927

14 Eichhorst, H. Ein merkwürdiger Fund im Blute eines Typhuskranken. *Deutsches Arch f klin Med* **14** 223, 1874

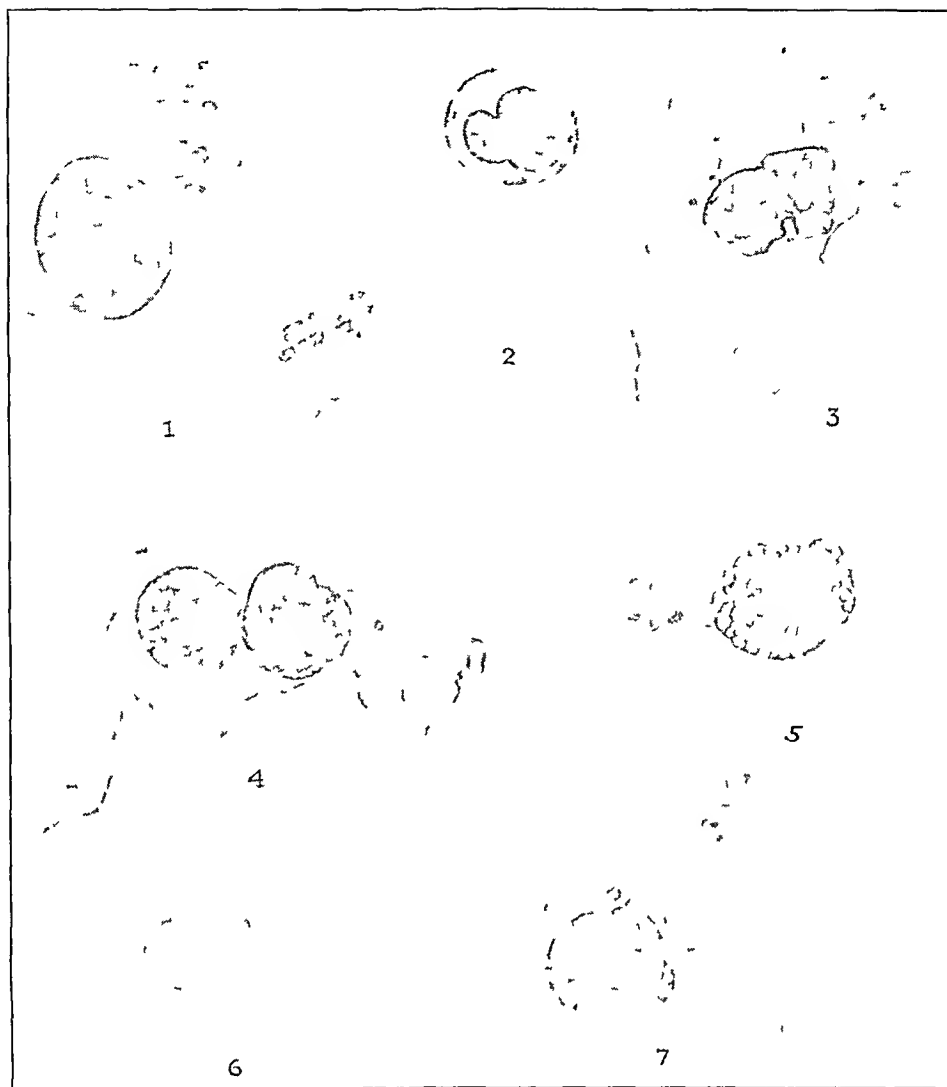
15 Rowley, M. W. The Occurrence of Atypical Phagocytic Cells in the Circulating Blood, *New York State J Med* **85** 674, 1907

16 Rowley, M. W. A Fatal Anemia with Enormous Numbers of Circulating Phagocytes, *J Exper Med* **10** 78, 1908

17 The rapidly developing anemia and the extremely high leukocyte count (800,000 per cubic millimeter before death) strongly indicate the diagnosis of monocytic leukemia. This would antedate by five years Reschad and Schilling's observation of the first reported case (Ueber eine neue Leukämie durch echte Uebergangsformen [splenozytenleukämie], *München med Wchnschr* **60** 198, 1913)

18 Van Nuys, F. An Extraordinary Blood. Presence of Atypical Phagocytic Cells, *Boston M & S J* **156** 390, 1907

19 Leede, W. Ein Fall von Endocarditis ulcerosa mit krankhaft entartenden Lymphozyten im Blut, *Mitt a d Hamb Staatskrankenanst* **12** 411 1911



Cells from preparations stained according to Wright's method, reduced from $\times 1,200$ Nos 1, 2 and 3 are from a case of dementia paralytica in which frequent convulsions occurred, 5, 6 and 7, from a case of monocytic (histiocytic) leukemia. No 1, an extremely large histiocyte. Several platelets seem to have become phagocytosed, the nucleolus in the spongy nucleus is prominent. No 2, an ordinary monocyte. The fine granules in the grayish-blue cytoplasm and the fine chromatin network of the indented nucleus are to be noted. No 3, a histiocyte with a large amount of ingested debris. Vacuole formation is common in these cells. No 4, the possible beginning of a giant cell. This has occurred in a histiocyte that has probably undergone amitotic division of the nucleus. Note the phagocytosed platelets and the vacuoles. The bizarre shapes of the cells 1, 3 and 4 are due to their marked motility and pseudopod formation, although cell 4 has probably become somewhat broken. No 5, the perfect histiocyte. Note the spongy character of the nuclear chromatin and the perinuclear arrangement of the granules. No 6, a cell apparently a transition between the typical histiocyte of 5 and 7 and the typical monocyte of 2. There are more pseudopod formation, a rounder nucleus and coarser granules than in the ordinary monocyte. No 7, another typical histiocyte seen in a more "active" stage than the cell 5. Nos 5, 6 and 7 were seen in one oil-immersion field in a case of monocytic leukemia.

bacterial endocarditis. This observation has been repeated by so many observers that the phagocytic histiocyte seems to have become identified with that disease. In 1912, Connal²⁰ found phagocytic cells in trypanosomiasis, malaria, smallpox and ankylostomiasis, he felt that the cells appeared while immunity was being acquired. Neukirch²¹ found cells containing pigment bile in a case of jaundice, and Kraus²² found phagocytic cells in a case of splenomegaly. Netousek²³ discovered these cells in cases of subacute bacterial endocarditis, typhoid fever and cholera and occasionally in other conditions, he also found suspected "Endothelien" at times in normal blood. In 1918 and 1919, Kaznelson²⁴ wrote the first general article on this subject and described the finding of histiocytes in a case of streptococcic pyemia and in one of general tuberculosis of the lymph nodes, in both of these cases hemorrhagic diathesis was present.

Kaznelson cited the finding of histiocytes by various authors in paroxysmal hemoglobinuria and in pernicious anemia. The first adequate descriptions of the cells are given by Ferrata and his associates²⁵. Ferrata called these cells "hemohistioblasts" and expressed the belief that they are the forerunners of all the blood cells. He and his associates pointed out the occurrence of these cells in the leukemias, especially in monocytic leukemia. Complete descriptions of the cell and of its spongy nucleus are given in these articles, which are excellently illustrated with colored plates. The first general article in the American literature is that by Simpson,²⁶ who studied the histiocytes exhaustively, mainly from the experimental standpoint. She was the first to study the cell systematically by the supravital technic. The subject is touched on by Naegeli²⁷ in his textbook and is discussed at greater length by

20 Connal, A. Auto-Erythrophagocytosis in Protozoal Diseases, *J. Path. & Bact.* **16** 502, 1911.

21 Neukirch, P. Ikterische Zellen im Blute bei Icterus neonatorum, *Ztschr. f. klin. Med.* **74** 380, 1911.

22 Kraus, F. Ein Fall von Splenomegalie, *Berl. klin. Wchnschr.* **50** 1421, 1913.

23 Netousek, M. Ueber Endothelien und ihre Beziehung zu den Monozyten, *Folia haemat.* **19** 1, 1914.

24 Kaznelson, P. Seltene Zellformen des stromenden Blutes (Megakaryocyten, Histiocyten, Endothelien), *Deutsches Arch. f. klin. Med.* **128** 131, 1918.

25 Franco and Ferrata (footnote 8). Reitano (footnote 9). Esposito, A. Morfologia e significato anatomico degli emoistioblasti nelle leucemia, *Haematologica* **4** 269, 1923. Ferrata, A., and Negreiros-Rinaldi. Emoistioblasti e monociti nella milza malarica, *Haematologica* **1** 243, 1920.

26 Simpson, M. H. The Experimental Production of Macrophages in the Circulating Blood, *J. M. Research* **53** 77, 1922.

27 Naegeli, O. Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin Julius Springer, 1923.

Schilling,²⁸ who was responsible for some of the earlier observations on the histiocyte, especially in malaria. Schittenhelm²⁹ gave a general review. Sabin and Doan⁷ studied the "clasmatocytes" with their supra-vital technic. Other papers of general interest are those by Richter³⁰ and Vasilu³¹.

MORPHOLOGY OF THE HISTIOCYTE

The most extensive work on the morphology of the histiocyte in fixed sections of tissue has been done by Maximow.³² Ordinarily two types of histiocytes are recognized: the reticular cell and the "endothelial" cell. These cells are large and contain large vesicular nuclei. The reticular cell differs from the endothelial cell in that it is situated in the stroma of various organs, its cytoplasm has long fibrillary processes that apparently bind together other cellular structures. These cells are characteristically seen in the spleen, bone marrow and lymph nodes. The endothelial cells line very small blood vessels or sinusoids in the liver, bone marrow, lymph nodes and spleen. There has been some discussion concerning whether or not these cells are identical with the reticular cells. Maximow³ expressed the belief that the grouping of endothelial cells about tiny blood vessels was more apparent than real. Together these two types of cells make up the reticulo-endothelial system.

Because the various processes involved in the fixation and staining of sections of tissue distort the cells to some extent, the morphology of the histiocyte is studied best in blood smears. In these preparations it is seen that the histiocyte is by far the largest of the circulating cells, measuring from 15 to 40 microns in diameter. Its shape is extremely variable, chiefly because of its marked powers of locomotion. It is usually oval, frequently it is round or polygonal, but it may be long and kite-shaped.³⁴ The cytoplasmic membrane is indefinite and usually shows budding or pseudopods, which often gives the cell a bizarre

28 Schilling, V. *The Blood Picture and Its Clinical Significance*, English edition, St. Louis, C. V. Mosby Company, 1929.

29 Schittenhelm, A. *Normale und pathologische Physiologie des retikulo-endothelialen Systems*, *Handbuch der Krankheiten des Blutes und der blutbildenden Organe*, Berlin, Julius Springer, 1925, vol. 2, p. 492.

30 Richter, M. N. Observations on the Hemohistioblast of Ferrata, *Am. J. M. Sc.* **169**: 336, 1925.

31 Vasilu, T. Sur la presence des cellules primitives migratrices dans le sang circulant, *Mem. de la Soc. de biol.* **88**: 934, 1923.

32 Maximow, A. *The Macrophages or Histiocytes*, in Cowdry, Edmund V. *Special Cytology*, New York, Paul B. Hoeber, Inc., 1928, vol. 1, chap. 14.

33 Maximow (footnotes 13 and 32).

34 On the basis of variations in size and shape, Sabin and Doan (footnote 5) divided these cells into four types: long, small round, large round and very large

appearance. In color, the cell is weakly basophilic; it stains sky blue with Wright's stain and it often has a "ground-glass" appearance. The granules, which are usually azure, are occasionally bluish; they are coarser than those in the monocyte. They are characteristically grouped about the nucleus, and are rarely found at the periphery of the cell.³⁵ There is often vacuolization of the cytoplasm, and phagocytosed particles are seen at times. The latter may be composed of fragments of cells or even of entire red blood cells, white blood cells or platelets as well as of bacteria or particles of pigment. When any of these particles are present, vacuoles are commonly seen. The nucleus is round or egg-shaped, usually it is centrally placed and is about one-half the size of the cell. Sometimes the nucleus is slightly indented, in which case the cell resembles more closely the ordinary monocyte. The nuclear membrane is distinct and heavy, and the nuclear chromatin is spongy in appearance, as Ferrata first pointed out. This spongy appearance is distinctive and, together with the other criteria, previously outlined, usually makes recognition of the cell easy.

At times, on account of the marked fragility of the cell, it appears to be broken up or to consist almost entirely of a nucleus with a faint and indefinite border of cytoplasm. In these cases, as Sabin and Doan³⁶ have pointed out, the definite nuclear membranes and the indefinite cytoplasm are usually enough to make the diagnosis of the cell possible.

Preparations supravivally stained by the method of Sabin³⁶ serve to emphasize interesting functional characteristics of the cell. It moves rapidly at a temperature of 37.5 C, so that there is continual shifting of the cytoplasm. Pseudopods constantly protrude, changing the cellular shape from oval to elongated and back again within a minute or two. Some of the shapes assumed are bizarre and account for the marked variation in appearance of the cell in stained preparations. At times, the cell is seen to surround a red blood cell or a group of blood platelets, which are then incorporated in its cytoplasm. When this occurs, the movements of the cell become extremely rapid, after a minute or two, vacuoles appear in the cytoplasm. As Kiyono³⁷ and Patella³⁸ pointed out, amitotic division of the cell rarely takes place; the cell divid-

35 Some authors, notably Ferrata and members of his school (footnotes 8 and 25) laid great emphasis on the color of the granules. Chiefly on the basis of these differences, they claimed to separate the histiocytes into various types—myeloid, lymphoid and monocytoid. These distinctions have not been made out in the present work. In fact, histiocytes from the same case may show marked differences in the staining characteristics of the granules.

36 Sabin, F. R. *Studies of Living Human Blood Cells*. Bull. Johns Hopkins Hosp. **34**: 277, 1923.

37 Kiyono, K. *Die vitale Carminspeicherung*, Jena, Gustav Fischer, 1914.

38 Patella, V. *La genesi endoteliale dei monociti, delle forme di passaggio e dei cosiddetti linfociti del sangue*, *Haematologica* **4**: 59, 1923.

ing into two parts which continue to move about as separate cells. There is a sprinkling of neutral red granules throughout the cell, these do not shift into the newly formed pseudopod unless the latter remains stationary for more than a few seconds. This lack of shifting of the granules into the periphery of the cell accounts for the characteristic central arrangement of the granules in the stained preparations. The mitochondria, which are brought out by the use of janus green, are seen as delicate filaments interspersed throughout the cytoplasm. The nucleus changes its shape readily with change in shape of the remainder of the cell. Grouping of the neutral red granules at the centrosphere may occur, but there is no characteristic grouping in the "Hof" of the nucleus as in the ordinary monocyte. In cases showing marked monocytosis and histiocytosis, cells may be seen that are apparently intermediate between the typical histiocyte and the typical monocyte. Accurate differentiation between the two then becomes impossible.

Staining of the histiocyte with oxidase by the method of Sato and Yoshimatsu³⁹ has given negative results in this work, although some authors found positive granules in certain cells. Doan and Sabin⁴⁰ said that the cells give positive results when stained with oxidase only if they contain ingested material that gives a positive reaction on staining. They suggested that the method used has probably a great deal of significance in the evaluation of results.

Cultures of the histiocytes have been made by Maximow,⁴¹ Avrorow and Timofejevski,⁴² the Lewises,⁴³ Bloom⁴⁴ and Carrel and Ebeling.⁴⁵

39 Sato, A, and Yoshimatsu S. Peroxidase Reaction in Epidemic Encephalitis. A New Diagnostic and Prognostic Method, *Am J Dis Child* **29** 301 (March) 1925.

40 Doan, C. A., and Sabin, F. R. Normal and Pathological Fragments of Red Blood Cells. Phagocytosis of These Fragments by Desquamated Endothelial Cells of the Blood Stream, The Correlation of the Peroxidase Reaction with Phagocytosis in Mononuclear Cells, *J Exper Med* **43** 839, 1926.

41 Maximow, A. Ueber die Entwicklungsfähigkeiten der Blutleukocyten und des Blutgefässendothels bei Entzündung und im Gewebeskulturen, *Klin Wchnschr* **4** 1486, 1925.

42 Avrorow, P. P., and Timofejevski, A. D. Kultivierungsversuche von leukamischen Blute. *Virchows Arch f path Anat* **216** 184, 1914.

43 Lewis, M. R. The Formation of Macrophages, Epithelioid Cells and Giant Cells from Leukocytes in Incubated Blood, *Am J Path* **1** 91, 1925. Lewis, M. R., and Lewis, W. H. The Transformation of White Blood Cells into Clasmatoocytes (Macrophages), Epithelioid Cells and Giant Cells, *J A M A* **84** 798 (March 14) 1925.

44 Bloom, W. Transformation of Lymphocytes of Thoracic Duct into Polyblasts (Macrophages) in Tissue Culture, *Proc Soc Exper Biol & Med* **24** 567, 1927.

45 Carrel, A., and Ebeling, A. H. The Fundamental Properties of the Fibroblast and the Macrophage. II. The Macrophage, *J Exper Med* **44** 285, 1926.

The technic of Rhoads and Parker ⁴⁶ was used in a case of monocytic leukemia, there was little variation in the cell except that it became much larger and more active, and it showed more phagocytosed particles.

The histiocyte must be distinguished chiefly from the ordinary monocyte, the large lymphocyte and the promyelocyte. The differentiating points have been grouped in table 1.

TABLE 1—Data on the Histiocyte and Its Differentiation

	Histiocyte	Monocyte	Large lymphocyte	Myeloblast	Promyelocyte	Polyomorphonuclear
Size (microns)	15-40	10-20	10-15	6-15	10-20	10-15
Shape	Variable	Oval	Longitudinal oval	Round to oval	Round to oval	Round
Pseudopods	Common	At times	Rare	Little "raps" at times	None	None
Cytoplasm Color	Sky blue	Grayish blue	Slav blue	Ultramarine blue	Blue, verging to pink	Pink
Granules	Azure, coarse, usually grouped about nucleus	Innumerable, fine, lilac	Large azure in 10 per cent of cells	Absent	Few large blue, red or violet	Many large blue, red or violet
Vacuoles	Common, phagocytosed material often present	Rare	None	Rare	None	Rare
Nucleus Size	About one half size of cell	Pelatively large	One half size of cell, eccentric	Fills almost entire cell	Large	Variable
Shape	Round to oval	Usually reniform	Usually round	Oval, rarely indented	Round	Polyomorphous
Character of chromatin	Spongy	Fine network	Thick blocklike masses	Extremely fine mesh	Coarse linear	Coarse linear
Nucleoli	Rare	Absent	Absent	1 to 5 in each cell	Occasional	None
Oxidase reaction	Negative	Fine, sparse positive granules	Negative	Positive	Positive	Positive
Supravital staining	Active amoeboid motion	Amoeboid motion, arrangement of granules	No motion	No motion	No motion	Granules move, "stream" and push cell

Thus the histiocyte is a definite cell with certain characteristic qualities—structural, tinctorial and physiologic. It is a cell that rarely appears in the blood stream. Its differentiation from other blood cells particularly from the monocyte, becomes difficult at times. The histiocyte and the monocyte often merge by almost imperceptible transitions. The

⁴⁶ Rhoads, C. P. and Parker, F. Jr. Observations on Incubated Normal Bloods, *Am J Path* 4: 271 (May) 1928.

histiocyte is thought by many to be the forerunner of the monocyte, and the collection of histiocytes throughout the body is called the reticulo-endothelial system

THE ORIGIN OF THE HISTIOCYTE IN THE BLOOD

There is still some difference of opinion as to the origin of the histiocyte in the peripheral blood, though the consensus is that it is a free cell of the reticulo-endothelial system. Sabin and Doan⁵ have maintained that the histiocyte is a fourth type of blood cell (the other types being the granulocyte, the lymphocyte and the monocyte), they have thus sharply separated the histiocyte from the monocyte. They expressed the belief that the monocyte is derived directly from the mesenchymal reticular cells, whereas the clasmatocyte is derived from the desquamation of endothelial cells that line the sinusoids in the liver, the bone marrow and the spleen or are present in diffuse connective tissue. Sabin and Doan⁵ observed, chiefly in embryologic studies, the direct dropping off of endothelial cells into the lumina of blood vessels with the subsequent appearance of histiocytes. They separate histiocytes from monocytes largely on the basis of their morphology as seen in supravital preparations, and they maintain that the histiocytes are present in blood from normal human beings (up to 4 per cent) in 80 per cent of blood counts. They felt that the constant desquamation of endothelial cells into the circulation is responsible for the appearance of the phagocytic cells, which are often seen as smudges or even as free nuclei in fixed preparations. On the other hand, the following objections may be raised to their conceptions: (1) lack of proof that the monocyte and the histiocyte are derived from separate sources, (2) the underemphasis of the fact that histiocytes appear in increased numbers in conditions in which monocytosis is present, (3) the lack of mention of cells that are apparently transitions between histiocytes and monocytes, and (4) the minimizing of the vast amount of work that has been done on the reticulo-endothelial system and that has shown chiefly that the "reticular" cell and the "endothelial" cell react in much the same way to dyes and other materials, and that they probably are variations of the same cell.

Since his original work in 1898, Mallory⁴⁷ has felt that new histiocytes (or endothelial leukocytes) are derived directly, even in the adult, from the endothelium lining ordinary blood vessels. This view has been strongly called into question by the work of Maximow,¹³ Evans³ and Aschoff,⁴⁸ and apparently it is not entirely accepted by Sabin and

47 Mallory, F. B. A Histological Study of Typhoid Fever, J. M. Research 3 611, 1898, Principles of Pathological Histology, Philadelphia, W. B. Saunders Company, 1923

48 Aschoff, L. Morphologie des retikulo-endothelialen System, in Schlittenhelm, A. Handbuch der Krankheiten des Blutes und der blutbildenden Organe, Berlin, Julius Springer, 1925, vol. 2, p. 473

Doan⁵ Maximow³² said definitely that the histiocytes of the blood were simply free cells of the reticulo-endothelial system

Ferrata⁴⁵ expressed the belief that the hemohistioblast—a primitive blood cell derived directly from the embryonic mesenchyme—is potentially the precursor of all blood cells, and that three types of circulating hemohistioblasts—myeloid, lymphoid and monocytoid—are distinguishable chiefly on the basis of difference in granules. It seems rather dubious that the granular hemohistioblast should lose its granules to form the nongranular myeloblast which later again takes on granules to form the myelocyte.

On the basis of an extensive experience in the culture of normal blood from numerous species of animals, the Lewises⁴³ concluded that histiocytes are more probably derived from monocytes than vice versa. They, as well as Cappel and Ebeling,⁴⁵ expressed the belief that monocytes and histiocytes are different phases of the same type of cell.

However, the following views generally accepted at present are that. The histiocyte is the generic name for the cells comprising the reticulo-endothelial system. Although the histiocyte may be potentially a precursor of all blood cells, it is usually incapable of much differentiation in adult life, except that it becomes a monocyte by direct transition or mitosis.⁴⁹ The histiocyte has the same relationship to the monocyte that the myelocyte has to the mature polymorphonuclear cell. There are not four types of blood cells, as Sabin and Doan maintained, but three.

A vast literature has accumulated on the subject of the reticulo-endothelial system, especially in the last few years. This literature has been adequately reviewed by Aschoff,⁴⁸ Schittenhelm,²⁹ Maximow,³² Krumbhaar,⁵⁰ Bloom⁵¹ and others. A widely scattered group of cells was incorporated into a "system" by Aschoff¹ and Kiyono after work

49 Schilling, V. Ueber hochgradige Monocytosen mit Makrophagen bei Endocarditis ulcerosa und über die Herkunft der grossen Mononuklearen, *Ztschr f klin Med* **88** 377, 1919. Weicksel, J. Ueber die grossen Mononuklearen und Uebergangsformen Ehrlichs (Monocyten) und ihr Verhalten bei Tuberkulose, *Med Klin* **16** 1326, 1920. Weill, P. Ueber Erythrophagocytose im stromenden Blute, *Folia haemat* **26** 27, 1920. Schittenhelm, A., and Erhardt, W. Untersuchungen über die Beziehungen des reticulo-endothelialen Systems zu den grossen Monocyten des Blutes mit Hilfe der Vitalspeicherung, *Ztschr f d ges exper Med* **46** 225, 1925. Paschkis, K. Zur Frage der Abstammung der grossen Mononuklearen, *Virchows Arch f path Anat* **259** 316, 1926. Masugi, M. Ueber die Beziehungen zwischen Monozyten und Histiozyten, *Beitr z path Anat u z allg Path* **76** 396, 1927.

50 Krumbhaar, E. B. The So-Called Reticulo-Endothelial System. *Internat Clin* **2** 280, 1925.

51 Bloom, W. The Origin and Nature of the Monocyte, *Folia haemat* **37** 1 (Oct) 1928.

with vital dyes by Ribbert,⁵² Goldmann⁷ and Tschachin⁵³ had shown the functional identity of these cells. Maximow⁴¹ studied intensively their embryologic and cultural qualities. Other investigations disclosed their importance in the abnormal storage of fat as in the lipoidemia of diabetes mellitus,⁵⁴ in lipoid histiocytosis,⁵⁵ in Gaucher's disease⁵⁶ and in xanthomatosis.⁵⁷ These cells were found to be concerned in the formation of bile from hemoglobin,⁵⁸ in the production of immunity against disease² and in the phagocytosis of bacterial organisms.⁴⁷ Reticulo-endotheliosis⁵⁹—leukemic and aleukemic—has recently been described, the leukemic form is generally known as monocytic (histiocytic) leukemia.⁶⁰

THE APPEARANCE OF HISTIOCYTES IN THE PERIPHERAL BLOOD

From the standpoint of pathologic physiology, it seems logical to search for histiocytes in the peripheral blood in any condition in which irritation of the reticulo-endothelial system—irrespective of its cause—is known to occur. Although Sabin and Doan⁵ found these cells in 80 per cent of normal subjects, they have not otherwise been described in normal conditions except by Uyeyonahara,⁶¹ who used a special supravital technic, and possibly by Netousek.²⁸ In an examination of at least 10,000 blood smears in the past three years histiocytes have not been found in normal persons. Their appearance was limited to the abnormal conditions described in the following paragraphs.

Monocytic Leukemia—Two cases of this rare disease were observed.⁵⁵ This disease was characterized by an acute course with the

52 Ribbert, H. Die Abscheidung intravenös injizierten gelösten Karmins in den Geweben, *Ztschr f allg Physiol* **4** 201, 1904.

53 Tschachin, S. Ueber die 'ruhenden Wanderzellen' und ihre Beziehungen zu den anderen Zellformen des Bindegewebes und zu den Lymphozyten, *Folia haemat* **17** 318, 1913.

54 Schultze, W. H. Ueber grosszellige Hyperplasie der Milz bei Lipoidämie (Lipoidzellenhyperplasie), *Verhandl d deutsch path Gesellsch* **15** 47, 1912.

55 Bloom, W. Splenomegaly (Type Gaucher) and Lipoidhistiocytosis (Type Niemann), *Am J Path* **1** 595, 1925.

56 Epstein, E. Beitrag zur Pathologie der Gaucherschen Krankheit, *Virchows Arch f path Anat* **252** 157, 1924.

57 Rowland, R. S. Xanthomatosis and the Reticulo-Endothelial System, *Arch Int Med* **42** 611 (Nov) 1928.

58 Haldeman, K. O. A Histologic Study of the Formation of Bile Pigment, *Arch Path* **7** 993 (June) 1929.

59 Sachs, F., and Wohwill, F. Systemerkrankungen des retikuloendothelialen Apparats und Lymphogranulomatose, *Virchows Arch f path Anat* **264** 640, 1927.

60 Dameshek, W. Acute Monocytic (Histiocytic) Leukemia, *Arch Int Med* **40** 718 (Oct) 1930.

61 Uyeyonahara, T. Studien über menschliche Blut-Histiozyten mittels vitaler Karminspeicherung in vitro, *Folia haemat* **40** 1, 1930.

appearance of from 70 to 80 per cent of histiocytes and monocytes. The leukocyte count before death in both cases was 140,000 per cubic millimeter. Studies with supravital staining were done, the histiocytes were extremely active, at times differentiation from the monocytes was very difficult. With Wright's stain, apparent transitions between the typical histiocytes and the typical monocytes could be made out. A postmortem examination was made in neither case, though studies on the bone marrow were carried out in the second case. In the other cases reported an intense proliferation of the reticulo-endothelial system with infiltration of the organs with histiocytes was always seen.

Agranulocytosis—This condition, in which the granulocytes disappear from the circulating blood, is probably due to direct action by bacteria or their toxins on the leukocytes of the bone marrow. It probably

TABLE 2—*Agranulocytosis*

Case	Date	White Blood Cells, per C. Mm.	Monocytes, per Cent	Histiocytes, per Cent
3	2/ 7/29	2,900	43.0	2.0
	2/ 8/29	4,650	49.0	6.0
5	5/11/29	880	60.0	5.0
7	12/27/29	8,000	28.0	9.0
	12/29/29	7,600	11.6	1.2
8	3/ 2/30	5,500	43.0	19.0
	3/ 3/30	5,500	33.5	15.0
	3/ 5/30	12,000	30.4	0.8
	3/ 6/30	10,000	10.0	0.0
	3/ 7/30	18,000	17.5	0.5
	3/ 9/30	15,000	12.0	1.0
	3/11/30	15,000	10.0	1.0

represents, not a disease entity, but an atypical reaction to sepsis. Secondary monocytosis has been reported frequently, though histiocytes have not as yet been described. At autopsy, enlargement of the spleen due at least partly to the proliferation of the reticulo-endothelial system has been observed. Nine cases of this disorder have been observed by me,^{61a} and in cases 3, 5, 7 and 8, histiocytes were found. In cases 7 and 8, in which recovery took place, there was marked monocytosis and histiocytosis during the phase of recovery. Monocytes and histiocytes numbered 28 per cent of the white blood cells in case 7 and 42 per cent in case 8. As the patient's condition improved, there was a decrease in the monocytic cells. This histiocytic-monocytic phase has recently been reproduced by Fried and me⁶² in rabbits suffering from experimental bacterial agranulocytosis.

61a Dameshek, W., and Ingall, M. Agranulocytosis (Malignant Neutropenia). *Am. J. M. Sc.* **181**: 502 (April) 1931.

62 Fried, B. M., and Dameshek, W. Experimental Agranulocytosis to be published.

Septicemia—Histiocytes have been observed in cases of generalized sepsis by Kaznelson,²⁴ Neukirch,²¹ Richter³⁰ and Schittenhelm²⁹ In the present study they were found in five cases of septicemia in which the organism was recovered from the blood stream before death The first three patients died In an overwhelming infection, the reticulo-endothelial system probably becomes stimulated, and histiocytes may appear in the circulation In these cases histologic examination of the spleen and bone marrow showed marked hypertrophy, an increase in the number of reticulo-endothelial cells and many phagocytic cells that often contained bacteria

In case 4, one histiocyte contained an inclusion body, probably a deteriorated red blood cell The immature polymorphonuclear cells noted were determined by the method of Schilling²⁸

Subacute Bacterial Endocarditis—As previously mentioned, histiocytes have been reported in cases of subacute bacterial endocarditis by numerous observers, so that the finding of these cells is considered of value in establishing the diagnosis The view has been prevalent that

TABLE 3—*Septicemia*

Case	Organism	Polymor phonuclear Leukocytes, per 100 Cc	Immature Neutrophils, per 100 Cc	Lympho cytes, per 100 Cc	Mono cytes, per 100 Cc	Histio cytes, per 100 Cc
1	<i>Streptococcus hemolyticus</i>	93.0	57.0	0.0	7	5.0
2	<i>Streptococcus hemolyticus</i>	93.0	40.0	4.0	3	2.0
3	<i>Streptococcus hemolyticus</i>	88.0	41.5	3.0	9	3.0
4	<i>Bacillus coli</i>	74.8	17.5	13.6	9	3.6
5	<i>Streptococcus viridans</i>	71.6	4.0	16.4	12	0.8

these histiocytes are desquamated endothelial cells of capillaries Therefore, in searching for them the customary advice has been to rub the ear vigorously for some minutes before making the blood smear, this presumably would dislodge some of the enlarged endothelial cells from the capillaries This concept has been vigorously attacked recently by Schilling²⁸ (compare also Aschoff⁶³ on this point), who demonstrated that most of the histiocytes, which are produced in large numbers in this condition, probably become infarcted or destroyed in the pulmonary capillaries, and the remainder are swept out into the general circulation

In the case of a patient, B. S., examination of the blood showed Jan 6, 1930, polymorphonuclear leukocytes, 67.2, immature forms of polymorphonuclears, 8.8, lymphocytes, 27, monocytes, 8, and histiocytes, 0.5, April 11, polymorphonuclear leukocytes, 57.5, immature forms of polymorphonuclears, 3, lymphocytes, 31, monocytes, 9.5, histiocytes, 0.5, eosinophils, 1.5, and basophils, 0.5 In S. C., examination of the blood on April 24, 1930, showed polymorphonuclear leukocytes, 84, immature forms of polymorphonuclears, 2, lymphocytes, 5, monocytes, 11, and histiocytes, 1

⁶³ Aschoff, L. Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924

Rheumatic Fever and Rheumatic Cardiac Disease—Monocytosis was observed in about 25 per cent of the cases of acute rheumatic endocarditis studied. Invariably, the monocytosis occurred at the beginning of the convalescent period, it was at this stage that histiocytes were occasionally found.

Tuberculosis—Although the blood picture has been studied in a fairly large number of cases of pulmonary tuberculosis, and although monocytosis is frequently present, histiocytes have been found in only one case.

In a patient, A. C., examination of the blood revealed polymorphonuclear leukocytes, 67, immature forms of polymorphonuclears, 28, lymphocytes, 10, monocytes, 21, histiocytes, 5, and eosinophils, 2.

Other Infections—Monocytosis⁶⁴ is commonly seen during convalescence from acute pyogenic infections, this is, in the "monocytic

TABLE 4—*Rheumatic Fever and Rheumatic Cardiac Disease*

Case	Date	Polymor phonuclear Leukocytes, per 100 Cc	Immature Cells, per 100 Cc	Lympho cytes, per 100 Cc	Mono cytes, per 100 Cc	Histio- cytes, per 100 Cc	Eosino phils, per 100 Cc	Baso phils, per 100 Cc
E. H.	3/20/29	65.5	4.0	25.0	7.0	3.0	3.0	
B. K.	9/16/29	62.5	28.5	14.0	21.5	4.0	1.5	0.5
H. N.	12/18/28	63.0	12.0	23.0	11.0	2.0		
G. N.	7/29/29	72.5	11.0	13.0	13.5	0.5		
W. S.	3/14/29	70.0	13.0	11.5	15.0	1.0		
A. A.	6/ 3/30	42.0	12.5	43.5	8.0	1.0		

stage of defense" of Schilling²⁸. It was during this period that histiocytes were occasionally discovered. Histiocytes were also found in other infections in which convalescence was not then taking place and in which monocytosis was not present.

Dementia Paralytica—In a study of the blood picture in seventy-five cases of dementia paralytica made in the Division of Research at the Boston State Hospital, histiocytes in varying numbers (from 0.4 to 6 per cent) were found in 20 per cent of all cases. This represents the first description of the presence of histiocytes in this disease. There is usually a direct correlation between the appearance of histiocytes and the presence of monocytosis of 12 per cent or over; there was no correlation with the treatment given. In none of the cases studied had malarial treatment been given for at least two years. As a matter of fact, it was often in the cases in which treatment had not been given for

⁶⁴ Monocytosis is considered present when the monocytes number 12 per cent or more of the total leukocyte count.

several years that histiocytes were commonly seen. Such a situation was observed in one remarkable case.

D. S., a man, aged 36, had acquired syphilis at the age of 20. A year later frequent convulsions developed, and he showed the neurologic and spinal fluid signs of dementia paralytica. Intensive treatment was begun, which was followed by a remission for five years. Convulsions then recurred, and they had continued to the time of writing. At the time of the first examinations (Nov. 4 to 7, 1929), from three to five convulsions occurred every night. The polymorphonuclear cells numbered from 20 to 22 per cent, the lymphocytes from 42 to 48 per cent, the monocytes from 28 to 40 per cent and the histiocytes from 1 to 6 per cent. The latter almost invariably contained phagocytosed material, such as red blood cells, platelets, etc., and were usually markedly vacuolated, of bizarre shape and

TABLE 5—Other Infections

Case	Condition	Poly morpho nuclear Leuko cytes, per 100 Ce	Im mature Cells, per 100 Ce	Lym pho cytes, per 100 Ce	Mono cytes, per 100 Ce	Histio cytes per 100 Ce	Posino phils, per 100 Ce	Baso phils, per 100 Ce
G. P.	Subsiding acute infection (? type)	86.0		1.5	12.5	1.5		
R. W.	Subsiding perinephric ab scess	66.6	12.0	16.0	12.5	0.5		
M. B.	Abscess of liver	84.0	18.4	8.4	7.6	1.6		
B. F.	Infectious monocyctosis	57.0	47.0	10.0	32.5	0.5		
R. M.	Subsiding mastoiditis	63.0	13.0	24.0	12.5	0.5	0.5	
M. S.	Subsiding ulcerative colitis	74.0	38.5	11.5	11.0	0.5		
S. H.	Chronic sinusitis	41.5		25.0	33.5	4.0		
J. A.	Subsiding infection (? type)	83.0	28.0	6.5	10.0	0.5		0.5
W. R.	Subsiding hepatitis	59.0		14.5	26.0	6.0		
W. G.	Subsiding mastoiditis	76.5	14.0	11.0	12.0	0.5		
B. B.	Subsiding acute appendicitis	40.5	1.0	37.5	14.5	0.5	7.5	

extremely active in supravital spreads. After large doses of phenobarbital had been given, the convulsions gradually ceased, and the differential count of the leukocytes became almost normal, the histiocytes disappearing. With the reappearance of convulsions, the differential count again became abnormal and histiocytes reappeared. Again the convulsions were stopped, and again the differential count became normal. At this point, a severe convulsion was induced by puncture of the carotid artery. Counts made before the convulsion were normal, but those made directly afterward were distinctly abnormal and showed the appearance of several histiocytes. There thus seemed to be a definite relationship between the presence of convulsions and the appearance of phagocytic histiocytes.

Blood smears from twenty-five patients with epilepsy failed to show histiocytes. It is interesting to speculate on the relationship of the convulsions to the appearance of the histiocytes. The possibility of increase in the reticulo-endothelial cells in dementia paralytica with consequent liberation of some of them as free histiocytes at the time of convulsion was considered.

Miscellaneous Conditions—Histiocytes were found in the miscellaneous conditions shown in table 6

The occurrence of histiocytes in these conditions chiefly in those in which the lymph nodes, the spleen or both were involved may be explained on the basis of the presence of large numbers of reticulo-endothelial cells in the aforementioned situations. Involvement of the spleen or lymph nodes from any cause may result in such marked reticulo-endothelial proliferation that histiocytes appear in the circulation. In the leukemias, histiocytes have been noted chiefly by Ferrata and by others of his school,²⁵ though they were first described in that condition by Rowley.¹⁶ In the case of trichiniasis previously noted,

TABLE 6—*Histiocytes in Miscellaneous Conditions*

Patient	Condition	Polymorpho nuclear Leukocytes, per 100 Cc	Immature Cells, per 100 Cc	Lymphocytes, per 100 Cc	Monocytes, per 100 Cc	Histiocytes, per 100 Cc	Eosinophils, per 100 Cc	Basophils, per 100 Cc	Prenucleo- cytes, per 100 Cc	Myeloblasts, per 100 Cc
F S	Anaphylactic enlargement of the lymph nodes	150	77	253	123	20				
E A	Lymphoblastoma of medi- astinum	705	30	110	175	20				
B S	Carcinoma of lung	460	30	290	235	25				
E	Carcinoma of lung	450	10	340	210	25				
W S K	Hodgkin's disease	615	40	250	130	20	05			
N P	Hodgkin's disease	670	25	140	105	25	75			
B S	Chronic hypochromic anemia, iron treatment	520		275	115	10				
H K	Chronic myelogenous leuke- mia	860	352	116	24	04				
R P	Acute myelogenous leukemia	28			02	02			04	948
I H	Trichiniasis	415	95	205	80	10	290	10		

biopsy of the deltoid and gastrocnemius muscles disclosed large numbers of multinucleated foreign-body giant cells with frequent mitoses of the numerous monocytoïd cells

THE CLINICAL SIGNIFICANCE OF THE APPEARANCE OF HISTIOCYTES IN THE PERIPHERAL CIRCULATION

Histiocytes in the peripheral blood have thus been observed in the following conditions: (1) leukemic proliferation of the reticulo-endothelial system (monocytic leukemia), (2) reactions to various infections namely, in septicemia, subacute bacterial endocarditis, rheumatic fever, agranulocytosis and dementia paralytica, and (3) miscellaneous conditions, particularly in the leukemias or in associated conditions. Except in the cases of severe septicemia in which the monocytes were relatively reduced, it was found that histiocytes tended to appear whenever monocytosis, generally of marked degree, was present. In these instances cells that presented morphologic characteristics midway between typical

histiocytes and typical monocytes were commonly seen. This evidence suggests that the histiocyte is the earlier cell in the monocyte series, just as the myelocyte (appearing in a severe pyogenic infection) is the earlier cell in the granulocytic series.

That the appearance of histiocytes in the peripheral blood represents either an overactivity or a disorder of the reticulo-endothelial system has not been entirely proved. Combined hematologic and pathologic investigations, however, in monocytic leukemia⁶⁵ and in the various infections, in monocytosis produced experimentally by *Bacterium monocytogenes*⁶⁶ or by *Bacillus coli*-like organisms⁶⁷ and in studies with vital stains¹ give strong indication that a monocytosis with the presence of histiocytes occurs when there is a proliferation of the reticulo-endothelial tissue.

This concept agrees with the observed clinical signs as previously pointed out. The reticulo-endothelial system apparently acts as a secondary line of defense against bacteria, the first line of defense being the polymorphonuclear cells. This is well brought out in the recovery phase of agranulocytosis, both clinical and experimental, and during convalescence from acute infections. As Metchnikoff² first pointed out, the macrophages are probably concerned with the development of immunity. The occurrence of histiocytes in the leukemias and in Hodgkin's disease may be explained on the basis of the close proximity or actual participation of histiocytes in the main cellular reaction, some of the histiocytes being pushed out into the blood stream.

SUMMARY AND CONCLUSIONS

1 The histiocyte has distinctive histologic and functional characteristics that make its presence in the peripheral blood stream easily recognized. In disorders that involve the reticulo-endothelial system, the histiocytes may appear in the peripheral blood usually coincident with an increase in monocytes. This is analogous to reactions of the bone marrow in which myelocytes appear in the peripheral blood coincident with an increase in polymorphonuclear cells.

2 Histiocytes in the peripheral blood were found especially when monocytosis was present. Thus they were seen in monocytic (histiocytic) leukemia, in agranulocytosis, especially in the phase of recovery, in septicemia, in subacute bacterial endocarditis, in the convalescent stage of rheumatic fever and rheumatic endocarditis, rarely in tuber-

65 Schwirtschewskaja, B. Ueber leukamische Retikuloendotheliose, Virchows Arch f path Anat **267** 456, 1928.

66 Lang, F. J. Zur Monozytenfrage, Folia haemat **36** 383, 1928.

67 Hoff, F. Ueber den Einfluss von Bakterienstoffen auf das Blut, Ztschr f d ges exper Med **67** 615, 1929. Fried and Dameshek (footnote 62).

culosis and other infections frequently in dementia paralytica (in one case associated with convulsions they were found in large numbers) and occasionally in miscellaneous conditions, especially in the leukemias and lymphoblastomas. Other authors have described their occurrence in typhoid fever, cholera, malaria, kala-azar and other diseases.

3 It is felt that the histiocyte as seen in the peripheral blood is a distinctive cell not normally present, that it is in intimate relationship and probably the direct precursor of the monocyte, though ordinarily without relationship to the other leukocytes of the blood, and that it appears in the peripheral blood when there is unusual activity, marked irritation or leukemic proliferation of the reticulo-endothelial system.

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Book Reviews

UEBER DIE AKUTE UND CHRONISCHE CLIBL LEBERATROPHIE MIT BESONDERER BERUICKSICHTIGUNG IHRE EPIDEMISCHEN AUSSETZENS IN SCHWEDEN IM JAIRE 1927 By PROF DR HILDING BERGSTRAND, Stockholm Price, 14 marks Pp 114, with 68 illustrations and 2 colored plates Leipzig Georg Thieme, 1930

In this monograph the author reports 150 cases of atrophy of the liver studied by him, 97 of which occurred during an epidemic in Sweden in 1927. The disease showed a remarkable tendency to appear at definite periods of the year, namely, spring and fall. It seemed to be epidemic, which led the author to believe that it was infectious. It was more prevalent in the cities, and more women than men were affected. Syphilis, treatment with arsphenamine and pregnancy apparently were only incidental predisposing causes.

The author draws attention to the marked clinical similarity of the course of catarrhal jaundice and that of acute yellow atrophy of the liver. It is only in the pulse rate that the two differ, the first having a bradycardia, whereas in the latter the pulse curve lies well above the temperature curve.

Results of pathologic studies conformed with the observations of other investigators. The degenerative process begins in the center of the lobule of the liver and may progress to various stages. Apparently those portions of the liver which have the greatest venous circulation are most involved. The region first attacked is that around the ligamentum falciforme hepatis. In the chronic forms, a cirrhosis results which may assume different aspects according to the character of the process. The author describes four types: (1) a large lobulated liver resembling a *hepar lobatum*, (2) a less coarse lobulation resembling the hobnail liver of Laennec's cirrhosis, and (3 and 4) types that display still finer irregularities of the surface.

The author also draws attention to the similarity of the course of acute yellow atrophy and that of glomerular nephritis. He suggests that in yellow atrophy the etiologic factor may be a streptococcus, the initial infection being in the upper respiratory tract. He describes a predilection of the disease for persons with a "rheumatic diathesis." Bacterial investigation of the intestinal tract of affected patients constantly showed *Streptococcus viridans*, but the disease has not been produced experimentally.

DIL PROCTO-SIGMOSKOPIE UND IHRE BEDEUTUNG FUR DIE DIAGNOSTIK UND THERAPIE DER KRANKHEITEN DES REKTUM UND DES SIGMOIDEUM By DR HERMANN STRAUSS, Berlin Second edition Price, 17.50 marks Pp 96, with 68 text illustrations, 1 schematic drawing and 9 colored plates Leipzig Georg Thieme, 1930

The author presents in an interesting manner the practical application of proctoscopic and sigmoidoscopic examination. In this work he has condensed the material in the first edition and has added new material.

He describes the methods of preparation of the patient and various positions for examination. His preference is the knee-chest position. A brief discussion of the anatomy of the rectum and sigmoid colon follows. The different types of instruments and their accessories are discussed and illustrated. The author prefers projected light rather than that which carries the light forward. In rare cases it is necessary to anesthetize the anus. The pathway of the tube up the bowel is described in detail. Although the author has never had the experience, perforation of the bowel has occurred and should be carefully avoided by being certain that the lumen of the bowel is ahead as the tube progresses.

Normal and pathologic observations at the various levels of the rectum and sigmoid colon are described and are beautifully illustrated in color. The indications and contraindications for proctoscopic examination are given the chief contraindications being peritonitis, infectious processes in the area contiguous to the rectum and sigmoid dyspneic patients and marked anemia. Finally the author discusses the use of the proctoscope in the treatment for disease by means of direct application of powders and sprays of various kinds. This procedure seems to be used quite extensively on the Continent.

This monograph is well adapted for teaching purposes and for those not entirely familiar with proctoscopic and sigmoidoscopic work.

HANDBOOK OF THERAPEUTICS By DAVID CAMPBELL, M.D. M.A. B.Sc., "Pollok" Lecturer in Materia Medica and Pharmacology in the University of Glasgow. Price \$4.50, net. Pp. 411, with 72 illustrations. New York: William Wood & Company, 1930.

The author's introduction points out the present difficulties in teaching therapeutics when he says: "The aim of the medical curriculum is to provide the student with sufficient knowledge to treat disease rationally, yet as a rule there is no part of his training with which the young graduate is more dissatisfied. He is taught Pharmacology and Therapeutics before he has had the opportunity of studying disease, he may even be instructed in therapeutics by one who though possessing a medical degree, has not himself any experience in the practice of medicine. To some extent, no doubt, this is made good in the clinic but it is too frequently the case that when the history and physical signs have been elicited, the diagnosis, differential diagnosis, and prognosis discussed, and the pathological aspect of the disease fully considered, the all important question of treatment is either ignored or is dealt with in such a perfunctory fashion that the student carries away no clear idea of the method of treating a similar case."

The book is concise and well written, including all types of treatments used at the present time, such as hydrotherapy, diets and all biologic products. In a book of this size it is, of course, impossible to go deeply into the different subjects and at the same time cover everything. Campbell has succeeded very well for the general practitioner, and for the intern it is a book well worth having.

ABDOMINO-PELVIC DIAGNOSIS IN WOMEN By DR. ARTHUR JOHN WALSCHIED. Price, \$12.50. Pp. 1,000. St. Louis: C. V. Mosby Company, 1931.

The author presents a comprehensive volume of 1,000 pages which covers well the field of abdominopelvic diagnosis in women. The index is rather extensive and is especially valuable in a work of this kind.

The book is well illustrated and brings out many important diagnostic methods. While the author gives nothing new in the method of presenting the material or in the subject matter, it is a valuable work in that it brings together in easily accessible form up-to-date knowledge that should be of definite help, especially to those who are not working continuously in the field of gynecology. It should be of great value to the student and will serve as a convenient reference work to the practitioner.

The paper and typographic work are excellent and the illustrations are for the most part well chosen and executed.

THE EVOLUTION OF CLINICAL NOSOGRAPHY. MEDICINE IN MODERN TIMES By KNUD FABER, M.D., LL.D., Professor of Internal Medicine, University of Copenhagen. With an Introductory Note by RUFUS COIL, M.D., Director of Hospital, Rockefeller Institute. Second edition. Price \$3.75. Pp. 222 with illustrations. New York: Paul B. Hoeber, Inc., 1930.

So few changes have been made in the text of the second edition of this interesting and stimulating book on the history of clinical description that the

reader may properly be referred to the original review (*ARCH INT MED* **33** 532 [April] 1924). A few paragraphs have been lengthened, and a few lines withdrawn. In chapter 4, reference is made to Widal's early emphasis on the value of spinal puncture, and Widal's portrait has been added. In chapter 5 (Functional Diagnosis), new material on metabolic tests replaces two pages of the 1923 edition. Unfortunately, the index has not been changed to correspond, certain names that have been dropped from the text are still carried in the index of the second edition. The format of the book has been substantially improved. The work may again be recommended to clinicians and students for its emphasis on a comprehensive view in the clinical delineation of a disease.

THE PATHOLOGY OF INTERNAL DISEASES By WILLIAM BOYD, M.D., M.R.C.P.
Ed. Dipl. Psych., F.R.S.C., Professor of Pathology in the University of
Manitoba, Pathologist to the Winnipeg General Hospital, Winnipeg, Canada.
Price, \$10. Pp. 837, with 298 engravings. Philadelphia: Lea & Febiger, 1931.

This volume is an important addition to the armamentarium of the student of internal medicine. It is an adjunct to the usual texts or treatises of internal medicine, but in no way supplants them. Throughout the work a correlation of pathologic anatomy, pathologic physiology and symptomatology is effected. The rationality of symptoms wherever possible is clarified by simple, logical and accurate description in excellent English. If one opens the book at any of the important chapters, one is immediately engrossed in the subject matter. There are numerous illustrations, which are excellently chosen and beautifully printed. The whole field of internal medical diseases, in contrast to those commonly considered surgical, is covered. There is, of course, some overlapping. There is a companion volume on "Surgical Pathology" by the same author.

It would be futile to attempt to describe any one chapter in detail. The chapters on the diseases of the heart, the kidneys or the thyroid, as examples, are especially well written. Sound ideas as to the classification of nephritis or of goiter are most convincingly presented. No text in the field of internal medicine that has appeared in recent years deserves more praise. It is different, readable, valuable as a reference book and in every way written from the point of view of the clinical teacher and practitioner.

MODERN METHODS OF TREATMENT By LOGAN CLENDENING. Fourth edition.
Price, \$10. Pp. 819. St. Louis: C. V. Mosby Company, 1931.

This book still remains the classic in the field of medical treatment for the practitioner and student. The lucid manner in which it is written and the fact that it includes every important field in medical therapeutics make it a necessary addition to any medical library. The author has not included every new phase of therapy in this edition, but has made a selection of the subjects that are well established by careful research or are in use by the leaders in the various fields. Among those included are the administration of salyrgan, the feeding of a stomach extract in pernicious anemia, the use of Calmette's tuberculin, the treatment for undulant fever and the chemistry of the thyroid action. The chapters on dietetics and the treatment for diseases of metabolism are particularly complete.

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